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Water requirements for renal excretion in full-term newborn infants and premature infants fed a variety of formulas

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CURRENTLY much emphasis is placed on the construction of infants' formulas with regard to their content of protein and solutes which are ultimately excreted by the kidney as end products of protein metabolism and electrolytes.[1-4] There is sufficient documentation to show[5, 6] that the average renal concentrating capacity in healthy, newborn premature infants and in full-term infants in the first few weeks of life is below that which is obtained later in life. For the purposes of this study, it is assumed to be 700 mOsm. per liter at a specific gravity approximating 1.021; this is about half the maximal renal concentrating capacity of the mature adult (1400 mOsm. per liter). Under usual circumstances of health and when the concentration of the solute load demanding renal excretion is below the maximal concentrating capacity of the kidney, "expendable" renal water is available. Under

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Table I. Average values* per liter

Formula	*Sodium (mEq.)*	*Potassium (mEq.)*	*Chloride (mEq.)*	*Milliosmols*	*Nitrogen (Gm.)*
Colostrum	23.8	18.8	28.7	285	5.4
Transitional breast milk	11.2	19.3	15.4	297	3.0
Low osmolar milk (Similac)	11.6	18.2	11.9	236	2.1†
Modified cow's milk	17.5	24.5	22.9	249	2.9
Whole cow's milk	23.1	36.2	32.9	286	5.1

*Average values of all samples prepared in milk laboratory and obtained from mothers by hand expression (colostrum and transitional breast milk).

†When dilution of Similac is prepared in biochemical laboratory instead of in routine milk laboratory, this value is 2.7.

these circumstances, the solute load of the formula does not place a demand upon body water which may result in dehydration. In the presence of severe dehydration, whether produced by deprivation or loss of water or by fever or high environmental temperature, a maximal urinary concentration may be expected with a decrease in expendable renal water. Thus with formulas resulting in a urine osmolar concentration significantly below 700 mOsm. per liter in the newborn and in the very young infant, a surplus of water above that obligated for solute excretion must exist. Under such circumstances it can be assumed that the formula being given the infant is satisfactory from the viewpoint of the renal water requirement. In instances where urinary concentrating capacity is greater than 700 mOsm. per liter, the amount of obligated renal water would be less; in circumstances where the concentrating capacity is below 700 mOsm. per liter, the obligated renal water would be increased.

This study is limited to full-term infants between the ages of 2 to 4 days and 6 to 9 days and to premature infants 10 to 56 days of age. These infants were fed a variety of formulas which contained different amounts of solutes demanding renal excretion to determine whether the resulting urine osmolarity was below the assumed maximal concentrating capacity for these infants.

METHODS AND PROCEDURE

The urinary osmolar excretions during the second to fourth days of life on various formulas were studied in 39 full-term newborn infants. The compositions of the formulas used are listed in Table I. Fourteen infants were fed modified whole cow's milk; 9, human milk (colostrum); 4, equal parts of evaporated milk and water; and 12, low osmolar milk formulas.* Three additional full-term newborn infants were studied during the sixth to ninth days of life while on human breast milk (transitional).† Seven premature infants varying in ages from 10 to 56 days were fed either low osmolar milk or equal parts of evaporated milk and water.

In the bottle-fed infants, the intake of formula was determined by the difference in bottle weight before and after feeding. In the breast-fed infants, the difference in the infant's weight before and after feeding was recorded as the intake.

Two consecutive, separate 24-hour collections of urine were made for each period of study. The urine was collected in a container surrounded by ice to minimize bacterial growth.

Daily analyses of the formulas were made with regard to their osmolar, sodium, potassium, chloride, and nitrogen contents. Osmotic pressures were determined with the Hill-Baldes apparatus.[7, 8] Sodium and potassium concentrations were determined with a Norelco flame photometer. Chloride was determined by the method of Sendroy modified by Van Slyke and Heller, and nitrogen

*Similac, Ross Laboratories.

†The formulas used in this study were prepared as follows:

Whole cow's milk —150.0 ml. evaporated milk, 150.0 ml. water.

Low osmolar milk (similac, Ross Laboratories)—8.5 Gm. dry milk, 60.0 ml. water.

Modified cow's milk —150.0 ml. evaporated milk, 16.0 Gm. Dextri-Maltose No. 1, 480.0 ml. water.

was determined by a Micro-Parnass-Wagner apparatus with the use of a 2 per cent boric acid solution with mixed indicator (bromcresol green and methyl red) and titration of the ammonia with sulfuric acid.

RESULTS

Table I lists the average composition of the various formulas used in the study. The data are derived from direct determinations. The values shown represent averages obtained from analyses of samples of the daily formulas as prepared in the hospital milk laboratory. It should be noted that the nitrogen value for the low osmolar milk is lower in the preparation made in the routine milk laboratory than the one prepared in the biochemical laboratory. The modified cow's milk formula fed the newborn infant was dilute when compared with the formula made of whole cow's milk. Whereas the carbohydrate in the various formulas adds to the total osmolar intake, it is not excreted in the urine and thus does not contribute to the total of solutes requiring renal excretion.

The substances in the formula which contribute mainly to the renal solute load are derived from protein and electrolytes; the excreted end product of protein metabolism is largely urea, which in feedings of whole cow's milk consists of about 40 to 60 per cent of the total osmolar excretion.[9] Low concentrations of osmols as derived from protein and electrolytes are found in transitional breast milk[10] and are closely comparable to those of the low osmolar milk formulas used in this study; conversely, the whole cow's milk formula and colostrum have higher osmolar concentrations. The osmolar values of the modified cow's milk formula was between these two feedings. The actual osmolar intakes are listed in separate tables.

Table II lists the intake and urinary output of fluid, electrolyte, nitrogen, and total osmols in full-term infants fed a formula of equal parts of evaporated milk and water. Each infant had a larger intake on the second day of the study, which is a reflection of the larger intake as the infant aged. The average intake for the 2 days was 106 ml. per kilogram per day. The average urine output of these infants was 24 ml. per kilogram per day, with an average osmolar excretion of 7.6 mOsm. per kilogram per day. It should be noted that with the increased intake on the second day of the study, there is an associated increase in osmolar excretion. There is, however, no consistent increase in urinary concentration of osmoles. The highest osmolar concentration on any given day was 449 mOsm. per liter and the lowest was 184 mOsm. per liter, with an average of 318 mOsm. per liter for the group. These values are well below those found by Hansen and Smith[6] in full-term

Table II. Intake and urinary osmolar excretions in full-term infants fed whole cow's milk*

Patient	Weight (kg.)	Age (days)	Fluid intake (ml.)	Urine output (ml.)	Sodium (mEq.)		Potassium (mEq.)		Chloride (mEq.)		Nitrogen (mg.)		Milliosmols		Urine (mOsm./L.)
					Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	
L. A.	4.1	3	73	11	1.69	0.14	2.58	0.39	2.31	0.19	361	71	20	3.8	355
		4	110	22	2.54	0.17	3.95	0.91	3.58	0.32	534	107	31	6.2	280
P. R.	4.2	4	86	18	1.97	0.46	3.00	0.70	2.70	0.65	447	80	24	5.4	306
		5	141	48	3.27	2.10	5.06	1.64	4.72	2.56	683	251	44	18.0	371
M. O.	2.8	3	75	21	1.74	0.20	2.72	0.62	2.36	0.51	391	57	21	3.9	184
		4	155	35	3.57	1.32	5.63	0.32	4.89	1.66	820	147	45	11.0	304
T. E.	2.8	2	75	8	1.74	0.34	2.70	0.33	2.60	0.40	402	63	21	3.7	449
		3	129	31	2.98	0.31	4.63	0.97	4.46	0.54	670	154	38	9.0	291
Average			106	24	2.43	0.63	3.78	0.74	3.45	0.85	539	116	31	7.6	318

*Per kilogram of body weight per day.

Table III. Intake and urinary osmolar excretions in full-term infants fed a low osmolar milk*

Patient	Weight (kg.)	Age (days)	Fluid intake (ml.)	Urine output (ml.)	Sodium (mEq.)		Potassium (mEq.)		Chloride (mEq.)		Nitrogen (mg.)		Milliosmols		Urine (mOsm./L.)
					Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	
H. A. L.	2.9	3	83	1	0.99	0.01	1.52	0.02	1.00	0.01	–	–	22	0.1	117
		4	98	5	1.22	0.11	2.01	0.10	1.17	0.03	–	–	25	0.9	170
B. R.	3.0	4	133	25	1.52	0.20	2.45	0.31	1.52	0.15	209	81	31	2.0	77
		5	173	37	1.83	0.56	3.18	0.34	1.80	0.41	432	61	43	3.0	79
M. A.	3.4	2	62	10	0.73	0.24	1.26	0.21	0.78	0.39	–	–	15	2.1	213
		3	91	16	1.05	0.19	1.70	0.33	1.08	0.25	–	–	23	2.7	175
S. T.	2.9	3	126	38	1.71	0.38	3.03	0.68	1.79	0.42	315	81	42	4.4	117
		4	135	63	1.49	0.75	2.48	1.01	1.61	0.63	308	50	30	6.3	100
Q. U.	2.3	4	222	78	–	–	–	–	–	–	364	89	51	6.8	87
B. R. Y.	3.3	2	73	20	0.86	0.08	1.41	0.22	1.15	0.12	188	70	19	1.9	91
		3	96	11	0.99	0.07	1.66	0.08	1.16	0.09	204	46	22	2.2	199
M. O.	3.3	4	146	41	1.60	0.12	2.68	0.33	1.59	0.33	261	74	32	3.7	90
		5	148	62	1.57	0.80	2.55	0.62	1.72	0.43	265	106	34	4.3	70
McD.	2.8	2	52	18	0.60	0.06	0.94	0.44	0.62	0.44	93	81	14	4.6	252
		3	89	35	1.04	0.04	1.65	0.46	1.06	0.49	197	112	17	7.9	225
L. A. N.	3.3	2	76	4	0.88	0.06	–	–	0.90	0.09	–	–	27	2.0	465
		3	83	4	0.97	0.05	–	–	0.99	0.10	–	–	28	1.8	492
B. O. Y.	3.2	2	110	30	1.28	0.09	2.00	0.39	1.31	0.09	–	–	19	3.0	101
		3	163	36	1.89	0.07	2.97	0.50	1.94	0.22	–	–	27	3.6	101
A. L.	3.2	2	137	20	1.59	0.14	2.49	0.34	1.63	0.10	–	–	22	3.0	150
		3	169	37	1.96	0.16	2.88	0.37	2.01	0.07	–	–	28	3.8	102
P. E.	3.3	2	120	11	1.39	0.04	2.18	0.13	–	–	–	–	29	1.5	141
		3	127	7	–	–	–	–	–	–	–	–	30	0.8	112
Average			118	27	1.30	0.20	2.20	0.40	1.30	0.20	258	77	27	3.2	157

*Per kilogram of body weight per day.

infants at this age during thirsting (approximately 600 mOsm. per liter).

Table III lists the intake and urinary output of a similar group of substances presented in Table II for full-term infants fed a low osmolar milk. The average total intake of this formula is slightly larger than that of whole cow's milk: 118 ml. per kilogram per day with an average osmolar excretion of 3.2 mOsm. per kilogram per day, about half of that observed with the infants fed equal parts of evaporated milk and water. The urinary osmolar concentrations average 157 mOsm. per liter; the lowest value is 77 mOsm. per liter and the highest is 492 mOsm. per liter. The average urinary concentration of 157 mOsm. per liter is significantly below that of infants fed equal parts of evaporated milk and water, 318 mOsm. per liter ($p < 0.05$). As with whole cow's milk feedings, these urinary osmolar values are considerably below the maximal renal concentrating capacity of normal full-term infants.

Table IV lists similar data for intake and urinary output of full-term infants fed a modified cow's milk formula. The average intake was 107 ml. per kilogram per day with an osmolar excretion of 5.2 mOsm. per kilogram per day. The average urinary osmolar concentration was 204 mOsm. per liter, which is significantly different from that in the infants fed whole cow's milk. The lowest value in this group is 114 mOsm. per liter and the highest is 446 mOsm. per liter. These values are also well under the maximal renal concentrating capacity of the normal full-term infant for this age.

Table V lists similar data for intake and urinary output for full-term infants fed human breast milk (colostrum). It is evident that the average total intake is significantly smaller in these infants than in the artificially fed infants; the average intake is 72.0 ml. per kilogram per day, with an osmolar excretion of 3.2 mOsm. per kilogram per day. The average urinary osmolar concentration was 273 mOsm. per liter, with a high value of 408. Again, these values are considerably below the maximal renal concentrating capacity for an infant of this age.

Table VI lists similar data for intake and urinary output of full-term infants fed human breast milk (transitional). The average intake is 162 ml. per kilogram per day, the largest of all the groups. These infants were 3 to 4 days older than the infants given the feedings listed above. The average osmolar excretion is 8.8 mOsm. per kilogram per day. The average osmolar urinary concentration of 122 mOsm. per liter is the lowest of the entire group. The lowest value obtained in this group is 77 and the highest is 194.

The second part of this study presents data on the patterns of excretion of premature infants from 10 to 56 days of age, whose weights varied from 1.4 to 2.1 kilograms. Table VII lists the intake and urinary output of fluid, electrolytes, nitrogen, and osmols in premature infants fed evaporated milk and water. The data in this chart come from a previous study.[9] The infants were maintained on this diet from 5 to 7 days prior to a 6-day study period. The data presented are average daily values. The average total intake is 149 ml. per kilogram per day, with an average urinary osmolar excretion of 26.5 mOsm. per kilogram per day, the average urinary concentration is 410 mOsm. per liter. These urinary osmolar concentrations are considerably below the maximal renal concentrating capacity of premature infants of this age.

Table VIII lists similar data for intake and urinary output of premature infants fed a low osmolar milk formula. The intake was 168 ml. per kilogram per day, with an average osmolar output of 8.7 mOsm. per kilogram per day, and an average urinary osmolar concentration of 104 mOsm. per liter, with a low of 81 and a high of 147. These values are well below the maximal renal concentrating capacity for these infants.

DISCUSSION

The nutritive value of the infant's formula is of paramount consideration in feeding. The purpose of this study, however, was primarily to determine whether constituents

Table IV. Intake and urinary osmolar excretions in full-term infants fed a modified evaporated milk and carbohydrate formula*

Patient	Weight (kg.)	Age (days)	Fluid intake (ml.)	Urine output (ml.)	Sodium (mEq.)		Potassium (mEq.)		Chloride (mEq.)		Nitrogen (mg.)		Milliosmols		Urine (mOsm./L.)
					Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	
S. I.	3.3	2	36	9	0.49	–	0.84	–	1.09	–	–	–	8	3.9	454
McK.	2.3	3	124	41	2.48	0.49	3.12	0.74	3.10	0.25	381	70	32	5.1	125
		4	163	74	2.93	0.96	3.98	1.11	3.60	0.74	535	169	41	9.9	134
T. H.	2.3	2	122	37	2.38	0.62	2.93	0.66	3.01	0.77	400	81	34	5.3	144
		3	131	32	2.54	0.55	3.13	0.64	3.04	0.74	419	122	35	7.4	230
M. U.	3.2	3	141	37	2.81	0.16	3.71	0.63	3.35	0.56	568	130	39	6.7	180
		4	141	66	2.63	0.66	3.32	1.12	3.40	1.31	482	188	34	11.1	169
W. H.	2.9	2	86	51	1.14	0.46	2.07	0.92	1.23	0.87	185	98	22	6.2	122
		3	104	40	1.81	0.20	2.54	0.88	2.37	0.60	300	74	28	5.0	124
B. E.	2.8	2	107	40	2.01	0.24	2.44	0.48	1.61	0.40	–	–	27	5.8	145
		3	154	27	3.44	0.21	4.05	0.33	3.91	0.30	–	–	40	3.6	132
B. E. C.	2.8	2	54	24	0.81	0.48	1.18	0.50	1.23	0.41	–	–	13	5.1	212
		3	116	15	2.11	0.39	3.20	0.26	2.66	0.23	–	–	32	2.8	180
B. O.	3.2	3	94	5	1.64	0.04	2.30	0.07	2.15	0.06	–	–	20	1.7	323
		4	106	31	1.86	0.43	2.60	0.86	2.43	0.89	–	–	29	4.4	145
H. A.	2.3	3	104	46	1.83	0.38	2.59	0.64	2.39	0.46	–	–	26	5.2	114
		4	148	55	1.68	0.82	3.62	0.99	3.39	0.99	–	–	37	7.2	131
E. U.	3.2	3	66	7	1.15	0.04	1.61	0.13	1.50	0.20	–	–	16	2.1	299
		4	80	13	1.40	0.15	1.95	0.19	1.73	0.21	–	–	22	2.6	201
J. A.	2.8	2	70	6	1.22	0.12	–	–	1.59	0.06	–	–	19	2.5	446
		3	86	19	1.50	0.25	2.10	0.56	1.96	0.27	–	–	21	5.8	302
S. E.	3.4	2	66	20	1.14	0.26	1.59	0.43	1.52	0.30	–	–	16	3.1	158
		3	102	22	1.92	0.26	2.50	0.46	2.32	0.20	–	–	25	4.0	184
L. I.	3.3	2	105	35	1.84	0.35	2.55	0.72	2.39	0.21	–	–	23	5.6	162
		3	133	67	2.48	0.73	3.81	0.67	3.06	0.52	–	–	36	10.5	158
D. E.	3.2	2	109	13	1.93	0.08	2.76	0.15	2.51	0.14	–	–	24	2.4	189
		3	141	20	2.70	0.14	4.05	0.12	3.22	0.20	–	–	38	3.1	156
Average			107	31	2.00	0.40	2.80	0.60	2.40	0.50	409	116	27	5.2	204

*Per kilogram of body weight per day.

Table V. Intake and urinary osmolar excretion in full-term infants fed human milk (colostrum)*

Patient	Weight (kg.)	Age (days)	Fluid intake (ml.)	Urine output (ml.)	Sodium (mEq.)		Potassium (mEq.)		Chloride (mEq.)		Nitrogen (mg.)		Milliosmols		Urine (mOs-m./L.)
					Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	
A. V.	3.2	2	33	3	0.80	0.07	0.63	–	–	–	–	–	9	1.7	–
		3	63	9	1.49	0.22	1.19	–	–	–	–	–	18	4.5	–
		4	66	18	1.56	0.54	1.23	–	–	–	–	–	19	6.5	361
G. I.	3.2	3	28	16	0.67	0.08	0.53	0.08	0.53	0.21	–	–	8	3.4	211
		4	81	9	1.93	0.09	1.53	0.15	2.33	0.04	–	–	23	0.9	97
L. Y.	3.3	3	36	5	0.87	0.04	0.74	0.83	0.68	0.03	174	–	11	1.3	242
		4	82	4	1.95	0.04	1.56	0.62	2.35	0.05	–	–	24	1.1	278
S. T. A.	3.3	3	64	46	1.50	–	0.90	–	–	–	340	59	–	3.0	70
K. E. L.	2.9	2	48	4	1.15	–	0.79	–	–	–	258	25	–	1.2	328
M. A. R.	2.0	2	100	7	2.38	0.11	–	–	2.87	0.08	864	51	29	2.7	408
		3		34	–	0.30	–	–	–	0.30	–	139	28	7.0	208
T. O.	3.2	4	103	32	1.96	0.16	1.85	0.28	–	–	405	78	30	4.1	127
		5	134	12	2.36	0.19	2.41	0.13	–	–	541	35	39	2.1	170
S. H.	2.8	3	96	19	2.61	0.27	1.44	0.22	–	–	1629	269	28	4.3	223
		4	73	32	1.75	0.33	0.88	0.29	–	–	–	–	21	4.6	–
G. R.	2.3	3	78	34	2.05	–	2.56	0.39	–	–	–	–	–	–	143
Average			72	18	1.60	0.20	1.30	0.30	1.80	0.12	602	94	22	3.2	273

*Per kilogram of body weight per day.

Table VI. Intake and urinary osmolar excretion in full-term infants fed transitional human milk*

Patient	Weight (kg.)	Age (days)	Fluid intake (ml.)	Urine output (ml.)	Sodium (mEq.)		Potassium (mEq.)		Chloride (mEq.)		Nitrogen (mg.)		Milliosmols		Urine (mOs-m./L.)
					Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	
L. A. S	3.2	6	117	86	1.5	3.4	2.2	1.0	–	–	342	167	34	14.1	164
		7	152	72	2.1	2.2	2.4	0.7	–	–	444	104	44	10.4	145
P. O. S.	3.4	7	79	26	1.0	0.3	1.4	0.1	–	–	335	90	23	5.0	194
G. L. D.	3.2	6	244	70	2.0	0.6	5.2	0.6	–	–	703	63	78	5.9	77
		7	220	108	1.7	0.7	5.1	1.2	–	–	635	112	64	8.6	80
Average			162	72	1.7	1.1	3.2	0.7	–	–	492	107	49	8.8	122

*Per kilogram of body weight per day.

in formulas commonly offered to infants would put undue demands on body water for the renal excretion of the metabolic end products of the diet. Among young infants there is a variability in the capacity of the kidney to excrete a solute load at a given rate and concentration. In the course of metabolism, the absorbed carbohydrate and fat in the diet are utilized by the body and do not become a part of the osmolar load excreted in the urine. On the other hand, ingested but nonretained protein is decomposed largely to urea and other osmotically active substances; their excretion by the kidney requires water. The electrolytes of the formula which are not retained also exert an osmotic effect and require water for renal excretion. Thus the protein and electrolyte

Table VII. Intake and urinary osmolar excretion in premature infants fed whole cow's milk*

Patient	Weight (kg.)	Age (days)	Fluid intake (ml.)	Urine output (ml.)	Sodium (mEq.)		Potassium (mEq.)		Chloride (mEq.)		Nitrogen (mg.)		Milliosmols		Urine (mOsm./L.)
					Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	
B. R.	2.1	56	151	67	4.50	2.78	5.28	2.98	–	–	900	475	50	36.2	540
C. L.	1.8	38	146	59	4.38	2.59	5.11	2.43	–	–	880	457	48	24.2	410
B. A.	1.6	28	150	68	4.50	1.07	5.25	2.69	–	–	900	403	49	19.1	281
Average			149	65	4.45	2.48	5.21	2.70	–	–	890	445	49	26.5	410

*Per kilogram of body weight per day.

Table VIII. Intake and urinary osmolar excretion in premature infants fed a low osmolar milk*

Patient	Weight (kg.)	Age (days)	Fluid intake (ml.)	Urine output (ml.)	Sodium (mEq.)		Potassium (mEq.)		Chloride (mEq.)		Nitrogen (mg.)		Milliosmols		Urine (mOsm./L.)
					Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	
G. H.	1.4	20	161	90	3.83	0.66	3.03	2.36	4.62	1.20	86	77	46	10.0	112
		21	186	91	4.43	0.51	3.50	4.16	5.34	0.94	100	104	54	9.7	106
K. E.	1.4	15	103	76	1.28	0.35	2.26	1.69	2.01	0.94	256	86	33	6.8	90
		16	113	89	1.33	0.41	2.48	1.89	1.87	0.91	286	101	33	8.0	90
C. L.	2.1	14	143	49	1.63	0.80	3.26	1.14	3.46	1.05	357	73	43	5.9	121
		15	172	62	2.09	0.89	3.71	1.83	2.70	1.35	441	102	49	9.1	147
L. A.	1.9	10	229	113	2.66	0.27	5.22	2.63	3.84	1.41	381	97	66	9.2	81
		11	234	130	2.72	0.39	5.76	2.79	3.98	1.45	400	120	67	10.9	84
Average			168	88	2.50	0.54	3.65	2.31	3.45	1.16	288	95	49	8.7	104

*Per kilogram of body weight per day.

Table IX. The average intake of the respective formulas

Age		Milk feedings	ml./kg./day
2 to 4 days	(full-term)	Whole cow's milk	106
2 to 4 days	(full-term)	Low osmolar milk	118
2 to 4 days	(full-term)	Modified cow's milk	107
2 to 4 days	(full-term)	Colostrum	72
6 to 9 days	(full-term)	Transitional milk	162
10 to 20 days	(premature)	Low osmolar milk	168
28 to 56 days	(premature)	Whole cow's milk	149

contents of the diet are the essential substances which must be considered in estimating the water needs of the infant for renal excretion. The data here presented indicate that the full-term newborn and older premature infant with an assumed renal concentrating capacity of 700 mOsm. per liter in an environment of 70° to 80° F. are quite capable of excreting the renal solutes derived from a variety of formulas, without requiring additional fluid intake or drawing upon stores of body water.

Table IX indicates the average intake of the respective formulas. Fig. 1 is a composite of the data presented in Tables II to VIII. The amount designated as obligatory renal water in the figure is predicated on the assumption that these infants can concentrate

their urine to 700 mOsm. per liter. The columns depict the urine output as a percentage of the intake. Each block represents an average of the percentage of urinary water excretion of all the infants in a single group. It is interesting that the renal water excretion in the full-term infants on the various diets was approximately 25 per cent of the intake (23 to 29 ml. per kilogram per day). Hansen and Smith[6] showed that infants of the same age, when thirsted, excreted about 10 to 15 ml. per kilogram per day. In the older full-term and premature infants, the urinary volume was 44 to 52 per cent of the intake. In these infants the actual total fluid intake per kilogram of body weight was larger than that of the younger ones. The figures in the solid portion of each column represent the amount of water in the urine unobligated by the excreted solutes (expendable renal water), indicating that this amount of water could have been reabsorbed by the renal tubules if needed for body economy. Thus in newborn infants fed whole cow's milk ad libitum with an average intake of 106 ml. per kilogram per day at 66 calories per kilogram per day, there was no drain upon body fluids and the renal excretion of water was beyond that demanded for the excretion of solutes. Those infants ingesting formulas with the smallest amount of osmols requiring renal excretion had a larger volume of expendable renal water. With the older full-term breast-fed infants ingesting an average of 162 ml. per kilogram per day, containing 105 calories per kilogram per day, there was a larger amount of unobligated water in the urine which could have been saved by the body if needed. In the 2 groups of older premature infants, those on the low osmolar milk had an average intake of 168 ml. per kilogram per day, while those on whole cow's milk had an average intake of 151 ml. per kilogram per day. There was a larger amount of unobligated or expendable renal water in the infants fed the low osmolar milk than in those fed whole cow's milk, yet even in the latter group, 45 per cent of the renal water was unobligated.

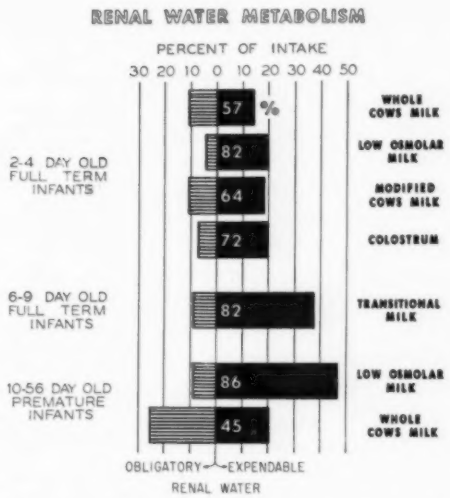

Fig. 1. The number in the solid area of each column represents the percentage of expendable renal water of the total urine output.

It must be emphasized that we do not recommend the feeding of undiluted, unmodified cow's milk to newborn infants. The margin of safety with such a formula with regard to the water requirements could be greatly reduced under adverse circumstances, when extra losses of renal water may be excessively large. In a previous study in premature infants[9] and in keeping with other data in the literature,[11, 12] it was demonstrated that the addition of a carbohydrate to an isonitrogenous diet increases the nitrogen retention and decreases the urea nitrogen excretion as well as the total renal osmolar excretion. These latter studies were short-term experiments, as have been most of the other studies on the protein-sparing effect of carbohydrate feedings. Nevertheless, they indicate that the addition of carbohydrate to the formula may be of value in sparing water during periods when the water balance of the individual is critical, when there may be depression of renal concentrating capacity, when there is a decreased intake of fluid or excessive losses of water. Whereas there is a variation in the total osmolar intake with various sugars in the diet, they do not have a variable effect on the amount of

water required for renal excretion unless they appear in the urine.

The above conclusions regarding unobligated renal water in the newborn infant during feeding with various formulas are predicated upon an assumed optimal renal concentrating capacity of approximately 700 mOsm. per liter and when extra renal water losses are *not* excessive. It is known, however, that some full-term newborn infants and older premature infants may concentrate to much higher levels.[9] It is also known that urinary concentrating capacity may be influenced by variations in the intake of dietary protein[16, 17]; it is reduced on a low protein intake and increased on a high one. Infants beyond the second month of life may give concentrations to adult levels of 1400 mOsm. per liter.[3] Under these circumstances when renal concentrating capacity is greater, the obligatory renal water volume will be smaller, resulting in a larger volume of expendable renal water.

In those instances where extra renal water losses are larger than usual, there will be a gradual diminution of unobligated renal water, and finally body stores will be drawn upon to meet the obligatory renal water needs. Cooke and co-workers[13] and Darrow and colleagues[14] have demonstrated that the extra renal water losses may be large when the infant is exposed to high environmental temperatures. There are conditions which may result in reduced renal concentrating capacity such as severe dehydration, potassium deficiency, infections, sickle cell anemia, primary renal disorders, etc. Under these circumstances, obligatory renal water demands would increase, and, when concentrating capacity is greatly reduced, the stores of body water may be depleted for renal solute excretion.

CONCLUSIONS

1. Full-term infants 2 to 4 days of age fed whole cow's milk, low osmolar milk, modified cow's milk, and human milk ad libitum and kept in an environment of 70° to 80° F., had a urine volume which measured approximately 25 per cent of the fluid intake. Fifty-seven per cent of the urinary water excretion of the infants fed whole cow's milk was expendable water; the highest amount of expendable water (82 per cent) was found in the infants fed low osmolar milk. These data indicate that in normal infants in this age period when extra renal water losses are not excessive, the ad libitum intake of the formulas studied do not impose a drain on the stores of body water.

2. In the 6- to 9-day-old full-term infants fed transitional human milk ad libitum, the urinary volume was approximately 45 per cent of the fluid intake; the intake of these infants was considerably larger than that of the 2- to 4-day-old infants. On this feeding, the expendable renal water was 82 per cent of the total urine volume.

3. Premature infants 10 to 20 days of age who weighed between 1.4 and 2.1 kilograms and who were fed low osmolar milk, excreted 52 per cent of their fluid intake, 86 per cent of which was expendable urinary water.

4. Even though a large proportion of the urinary water excretion of full-term newborn infants and 10- to 56-day-old premature infants when fed a formula of whole cow's milk is expendable, the margin of safety with such a formula with regard to water requirements would be greatly reduced when extra renal water losses are excessive. We, therefore, do not recommend the feeding of undiluted whole cow's milk at this age period.

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The renal excretion of water in infants immediately following operation

I. Surface surgical procedures

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WITH THE TECHNICAL ASSISTANCE OF

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IN ADULTS, following general anesthesia, there is some evidence of limitation in the renal excretion of water during the first postoperative day.[1, 2] Conversely, in hydrated infants, Calcagno and co-workers[3] could not demonstrate such a limitation. Data concerning this problem would seem essential for the appropriate administration of fluids to infants undergoing operation. The experiments to be presented were designed to study the renal ability of infants to excrete water in the immediate postoperative period and to attempt an evaluation of some of the variables inherent in any surgical procedure that may be important in conditioning this renal response.

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MATERIAL AND METHODS

Water loads comprising 3 per cent of the patient's body weight were administered intravenously to a group of male infants ranging in age from 3 to 27 months. These infusions were begun within 82 minutes following surface* surgical procedures. Periods of 90 minutes were allowed for the administration of the initial water loads to provide ample opportunity for glomerular filtration rates to return to preoperative values.[4, 5] Following the initial load, a sustaining infusion was maintained at rates calculated to replace estimated insensible and measured renal losses of water in order to maintain a positive water balance. Solutions of 3 or 5 per cent glucose in water were used as the infusion fluid. Urine collections were obtained from most patients during the postoperative

*Superficial operations such as herniorrhaphy, tonsillectomy, etc., in contradistinction to an intra-abdominal or intrathoracic operation.

studies by means of an indwelling urethral catheter. Air was instilled into the bladder at the end of each collection period to assure complete emptying.

Serial determinations of urine creatinine, osmolality, and volume, and of serum creatinine, sodium, and osmolality were obtained. A Baird internal lithium standard flame photometer was used for sodium analyses. Urine and serum osmolalities were determined on a Fiske osmometer with the use of 2 ml. samples. Creatinine was determined by the method of Hare.[6]

Free water clearances (C_{H_2O}) were calculated by the formula $C_{H_2O} = V \text{ ml./min.} - \left(\frac{U \text{ mOsm./L.} \times V \text{ ml./minute}}{P \text{ mOsm./L.}}\right)$ where V is the urine flow in milliliters per minute, U the osmolality of the urine in milliosmols per liter, and P the osmolality of the serum in milliosmols per liter. The latter part of the equation $\left(\frac{U \text{ mOsm./L.} \times V \text{ ml./minute}}{P \text{ mOsm./L.}}\right)$ is termed the osmolal clearance. It represents the minimal amount of water excreted per minute required to enable the solutes excreted in the same time period to exist in a hypothetical solution which is isosmotic with plasma. Any water excreted in excess of this amount is termed osmotically "free water." The absence of the excretion of "free water" during the period of observation following water loading was assumed to be evidence of persistent postoperative antidiuretic activity provided the glomerular filtration rate was not depressed and extracellular hypotonicity had been produced by the water load. The excretion of "free water" under these conditions was accepted as qualitative evidence for the absence of antidiuretic effects.

Endogenous creatinine clearances were measured to estimate changes in glomerular filtration rates.

The patient's response to a water load administered at a time unrelated to the operation served as his control observation. The water load during the control period was administered by the oral route in some patients. When the oral and intravenous routes were compared in normal human beings, no significant differences in the magnitude of the water diureses could be demonstrated.[7]

RESULTS

Table I illustrates some of the clinical and laboratory data. No special efforts were made to hydrate 5 infants prior to or during the operation (Patients 1 to 5, inclusive). They all lost significant amounts of weight and were known to have had inadequate fluid intakes preoperatively. They all exhibited delayed responses to their postoperative water loads. To eliminate the role of dehydration which was present in these first 5 patients, 7 other infants were hydrated prior to and during operation (Patients 6 to 12, inclusive). Their responses to the postoperative water loads were characterized as either prompt, partially delayed, or delayed. The data concerning the individual response patterns are presented in detailed form in Table II.

Fig. 1 presents the data obtained on 1 hydrated patient in the immediate postoperative period (Patient 7, A. C.). The isotonicity level is the average value for serum osmolality observed in our laboratory. The prompt appearance of urinary "free water" and the relative status quo of the serum sodium and osmolality that were observed in this patient would be those expected in any healthy, hydrated infant subjected to such a water load at a time unrelated to operation.

Fig. 2 contains the data obtained on another hydrated patient postoperatively (Patient 12, A. G.). The glomerular filtration rate rapidly returned to relatively normal values and yet there was a delay in the production of hypotonic urine and hence osmotically "free water." This delay in excretion of free water is associated with a fall in the serum osmolality and is indicative of a delayed water diuresis and some abnormal retention of water. A response to the postoperative water load did occur within a few hours as indicated by the eventual appearance of urinary "free water." It is of interest to note the sudden production of hypertonic urine following the painful replacement of

Table I. Data on individual patients

Patient	*Age (month)*	*Surface area (M^2)*	*Preanesthetic agent*		*Anesthesia**		*Surgical procedure*	*Response to post-operative H_2O load*
			Dose (grains)	*Minutes before operation*	*Length (minutes)*	*Remarks*		
Nonhydrated								
1. (T. C.)	3	0.28	Atropine 1/400	35	70	Smooth	Bilateral inguinal herniorrhaphy	Delayed
2. (A. Bo.)	9½	0.43	Nembutal ½ Morphine sulfate 1/72 Scopolamine 1/450	100	60	Smooth	Bilateral inguinal herniorrhaphy	Delayed
3. (A. Ba.)	12	0.48	Nembutal ½ Morphine sulfate 1/72 Scopolamine 1/450	51	64	Laryngospasm at induction	Bilateral inguinal herniorrhaphy	Delayed
4. (D. R.)	16	0.51	Nembutal 1 Morphine sulfate 1/72 Scopolamine 1/360	45	65	Smooth	Bilateral inguinal herniorrhaphy	Delayed
5. (J. W.)	16	0.52	Nembutal 1 Morphine sulfate 1/48 Scopolamine 1/300	60	35	Smooth	Excision of thyroglossal cyst	Delayed
Hydrated								
6. (J. F.)	26½	0.62			75	Smooth	Umbilical herniorrhaphy	Delayed
7. (A. C.)	5	0.43	Atropine 1/400	60	70	Smooth	Excision of branchial cleft cyst	Prompt
8. (J. L.)	13	0.45	Nembutal ½ Scopolamine 1/300	125	130	Smooth	Excision fatty tumor left arm	Delayed
9. (J. B.)	7	0.36	Nembutal ½ Atropine 1/300	60	65	Slight secretions	Bilateral inguinal herniorrhaphy	Partially delayed
10. (R. H.)	22	0.56	Nembutal 1 Morphine sulfate 1/96 Atropine 1/250	150	100	Smooth	Bilateral inguinal herniorrhaphy	Partially delayed
11. (A. S.)	1	0.24	Atropine 1/400	80	50	Smooth	Right inguinal + umbilical herniorrhaphy	Prompt
12. (A. G.)	27	0.48	Nembutal 1 Morphine sulfate 1/64 Atropine 1/300	50	55	Smooth	Unilateral inguinal herniorrhaphy	Partially delayed

*All patients received N_2O, C_3H_6, and ether and all patients maintained at Plane 1 of Stage 3.

Table II. Response patterns to postoperative water loads

Patient	Serum osmolality (mOsm./L.)			Urine osmolality (mOsm./L.)					C_{inu} maximum (c.c./min./M^2)	Time* glomerular filtration rate reached 80% of control value	Time (min.) H_2O load initiated after end of anesthesia	Duration of observation after anesthesia (minutes)
	Postoperative	Maximum depression	Time*	Postoperative	First hypotonic specimen	Time*	Lowest osmolality	Time*				
Nonhydrated												
T. C.	292	278	340	584	245	292	130	247	2.5		55	340
A. Bo.	291	271	170	900	None		300	340	None		45	360
A. Ba.	276	267	300	460	None		415	190	None		55	300
D. R.	143†	129†	315	1260	150	228	100	327	3.2	12	82	360
J. W.	286	263	270	580	180	150	180	150	0.9	54	63	270
Hydrated												
J. F.	278	258	290	670	165	145	50	250	7.9	60	78	290
A. C.	142†	136†	54	395	95	105	50	54	12.0	12.0	24	210
J. L.	278	255	240	660	None		340	170	None	15	30	240
J. B.	282	259	196	580	260	74	260	74	0.1	36	18	196
R. H.	282	268	120	550	140	95	38	180	7.1	96	18	225
A. S.	285	279	105	190	190	0	48	50	7.3	87	9	168
A. G.	281	263	216	390	110	93	53	100	7.8	28	15	216

*Minutes after start of postoperative H_2O load.

†Serum sodium.

the patient's urethral catheter. This phenomenon of temporary antidiuresis following painful or traumatic experiences has been demonstrated by others.

The data from another hydrated infant in the immediate postoperative period are recorded in Fig. 3 (Patient 8, J. L.). As in the previous patient (Fig. 2), there is a prompt return of the glomerular filtration rate to relatively normal levels and yet a failure to produce hypotonic urine in spite of marked decreases produced in the levels of serum sodium and osmolality. The length of the period of antidiuresis prompted the designation of this response as delayed.

Individual values for serum sodium or osmolality levels are plotted in Fig. 4 in respect to the time they were obtained after the start of the water load. A relationship between delays in the renal response to the water load and depressions in serum sodium (or osmolality) levels is evident.

Fig. 5 contains data concerning the rates of glomerular filtration. It can be seen that the clearances of creatinine rose to relatively normal control values within 1 to 2 hours in all patients. Hence this could not account for the delay in excretion of hypotonic urine that was observed in some patients. All but 2 specimens of urine were hypotonic by the sixth postoperative hour. The 2 exceptions were approaching the isotonicity level when the observations were concluded at 200 and 260 minutes, respectively, after operation.

DISCUSSION

There is evidence that some preanesthetic and anesthetic agents can produce a temporary period of antidiuresis.[8, 9, 10] Aprahamian and colleagues[10] have shown that induction with ether, nitrous oxide, or cyclopropane regularly caused abrupt and long-lasting inhibition of a previously established water diuresis. The use of these 3 anesthetic agents in the present study cannot account for the different responses that were observed since every patient received all 3 agents (i.e., ether, cyclopropane, and nitrous oxide). The depth of anesthesia was maintained at Plane 1 of Stage 3 (light surgical anesthesia) in every patient. In addition, no relationship seems evident between the type of preanesthetic agent used or the time that elapsed

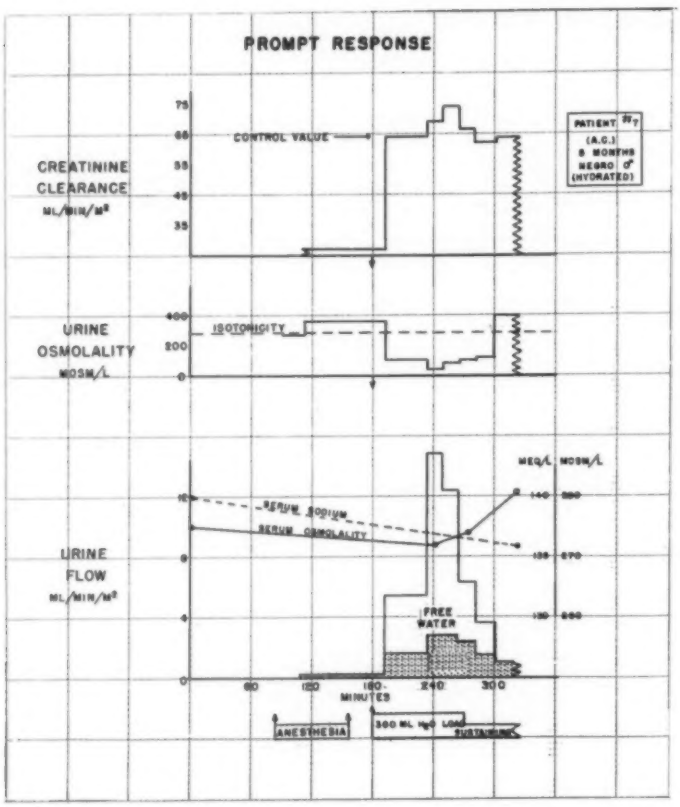

Fig. 1.

between the administration of these agents and the induction of anesthesia and the renal response (Table I). The types of surface surgical procedures were notably similar in all 12 patients. Differences in the length of anesthesia did not seem to be related to variations in the renal responses. The presence of prior water deficits in the nonhydrated group indicates that this factor can be responsible for postoperative antidiuresis even in response to a water load. The reason(s) for variation in promptness of onset of renal water diuresis in the group of hydrated infants remains unknown.

We interpret the production of hypotonic urine by the sixth postoperative hour as evidence that the cause or causes of any preexisting antidiuretic state were no longer operative. If so, it would appear that the major potential danger period in respect to the occurrence of water intoxication due to an inappropriate antidiuretic state in infants after a surface operation is probably limited to the first 6 postoperative hours.

The failure of some hydrated infants to excrete the postoperative water loads promptly would seem to be at variance with the results obtained by Calcagno and associates.[3] The difference is more apparent than real, however, since the 5 hydrated infants in their study were not tested during the first 6 hours postoperatively.[11] Their results may be taken as additional evidence that any antidiuretic period that exists appears to end prior to the sixth postoperative hour.

These results following a surface operation cannot be used to predict the patterns of renal water excretion in infants following

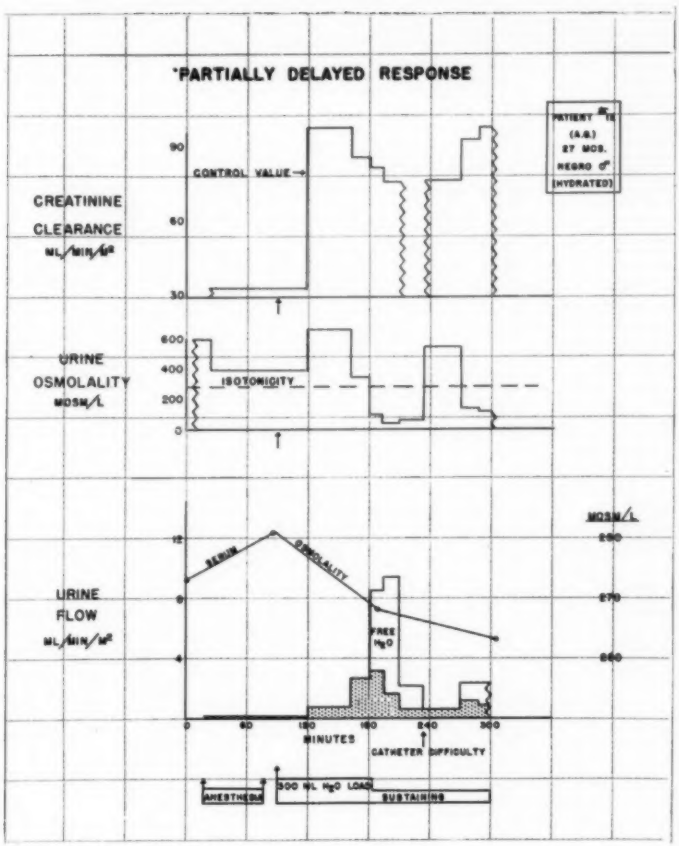

Fig. 2.

a prolonged, major operation. When one considers the study of Harned and Cooke,[12] he would suspect that a period of antidiuresis might occur and persist beyond 6 hours postoperatively. Their data, however, are far from conclusive and only serve to indicate that the problem of the renal handling of water by infants following prolonged operation merits further investigation.

Similar data concerning the newborn infant are conflicting. Colle and Paulsen[13] could demonstrate no retention of water during the first 24 postoperative hours while Rickham[14] felt that some water retention did occur. In neither study were the postoperative collections of urine divided into 6- or 12-hour periods in order to determine whether an early period of antidiuresis might have occurred. Only enough fluids were given in these two studies to ensure hydration. Discrete studies of renal water excretion of newborn infants in the postoperative period will require the administration of larger quantities of water.

As a corollary it should be noted that no deleterious clinical effects were observed from either an anesthetic or surgical point of view in the 7 patients in whom considerable efforts were made to assure adequate hydration before and during operation.

It would be unusual for an infant under ordinary circumstances to receive as much fluid in such a short period of time postoperatively as was administered in this study

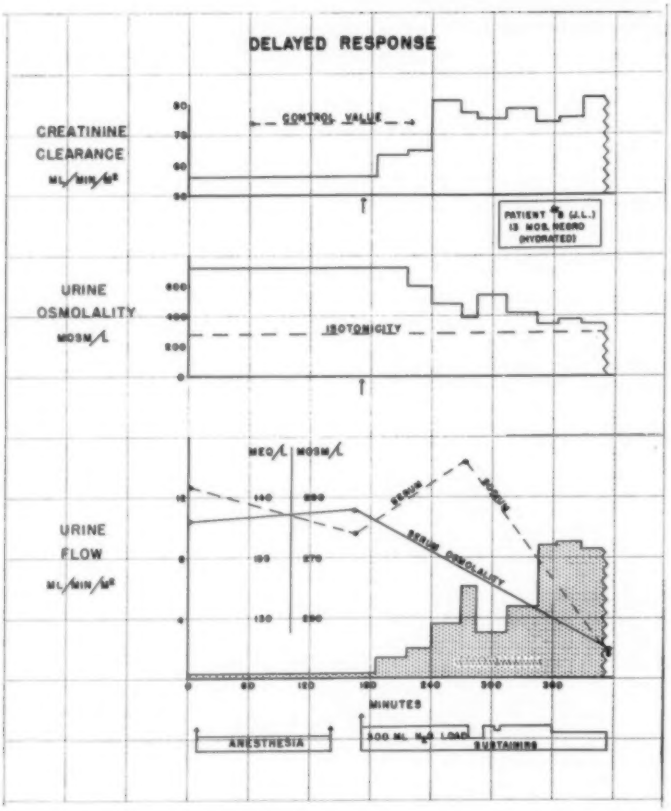

Fig. 3. No value for serum osmolality was obtained at 275 minutes. In view of the elevation of the serum sodium at this time, it also would have had to have risen proportionately. Therefore the smooth downward slope of the serum osmolality line is somewhat misleading.

(3 per cent of body weight in 90 minutes). Hence, in the period immediately following a surface operation, the use of *reasonable* amounts of fluid would not be contraindicated from the data obtained in this study.

SUMMARY AND CONCLUSIONS

1. Five patients, in whom no steps were taken to insure hydration before or during a surface operation under general anesthesia, all exhibited delayed diuretic responses to postoperative water loads administered within 82 minutes following the cessation of anesthesia.

2. In 7 other infants, in whom adequate preoperative hydration was accomplished, this period of antidiuresis was not eliminated completely in all cases during the first 6 hours following surface surgical procedures under general anesthesia.

3. When a transitory period of antidiuresis occurred in the hydrated infants, it was not associated with significant depressions of glomerular filtration rates, with the type or duration of anesthesia, or with the type of preanesthetic agent administered.

4. When a period of antidiuresis occurred in hydrated infants, it appeared to exist no longer than 6 hours postoperatively.

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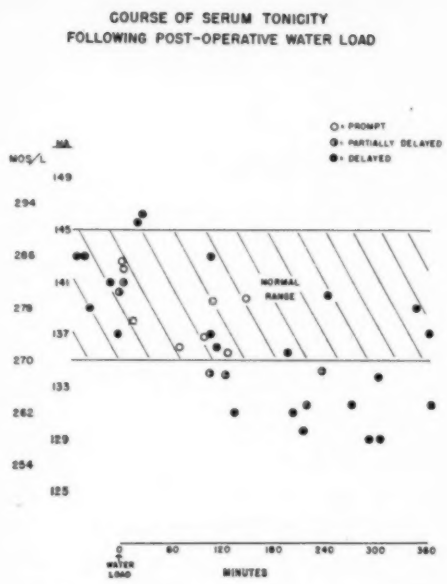

Fig. 4.

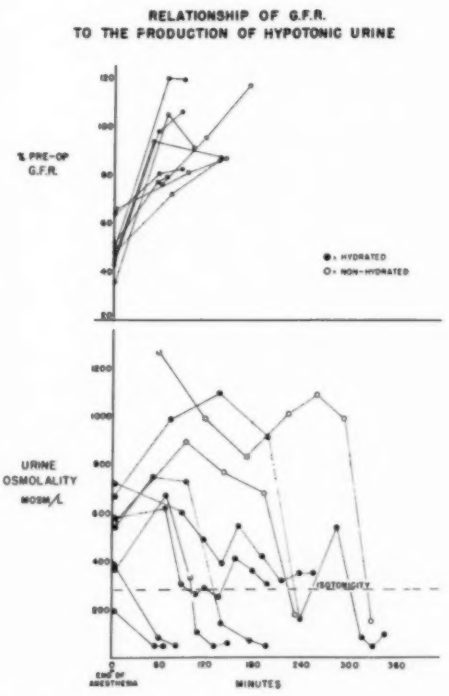

Fig. 5.

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Paragonimiasis in children in Korea

Related to the custom of ingesting raw crayfish for the treatment of measles

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IN THE last decade a new clinical entity in infants and young children has been described which is characterized by a persistent high eosinophilia with leukocytosis, hepatomegaly, hyperglobulinemia, and pulmonary infiltrations. Considerable speculation has existed in regard to the cause of this syndrome, but most authors agree that the pathologic process is probably the result of hypersensitivity.

In 2 cases[1, 2] the offending larva was assumed to be that of *Ascaris lumbricoides,* but Beaver and his associates[3] identified them as Toxocara. Beaver and co-workers were the first to prove experimentally that larvae of nematodes naturally adapted to hosts other than man can remain immature in the human host for a long time and can cause the manifestations of this syndrome. Brill[4] identified a larva of Toxocara in a nodule of the pleura. Milburn and colleagues[5] and Karpinski and his associates[6] also reported cases attributable to *Toxocara canis* on the basis of biopsies of the liver. They have shown that this syndrome is caused by the ingestion of embryonated ova of dog or cat round worms.

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The purpose of this paper is to summarize the clinical observations made on 8 children whose symptoms were strikingly similar to those of visceral larva migrans but who were reported to have paragonimiasis resulting from the ingestion of raw crayfish for the treatment of measles.

SYMPTOMATOLOGY

The ages of the patients to be presented varied from 2 years and 10 months to 11 years and 3 months; all of them were males. In most instances, there was a striking uniformity in the mode of onset which was rather insidious. The onset of the disease in those with mild cases was not readily apparent but became evident with slight cough, mild fever, and malaise so that in each instance the diagnosis of pulmonary tuberculosis had been made at private clinics. In moderate or severe cases the incubation period was thought to be 20 to 30 days. The onset was characterized by fever, cough, and wheezing; however, in the severe cases there were generalized convulsions associated with high fever. The illness in most of the severe cases was also diagnosed as pulmonary tuberculosis at other hospitals or private clinics. Cough, wheezing, and fish-smelling, rusty sputum are also said to be character-

istic symptoms of paragonimiasis in adults. Three of the 8 patients had a moderate to marked hepatomegaly with various amounts of ascites; 7 of the 8 had a mild to marked pleural effusion, and 1 of them had a massive empyema. One patient had pericardial effusion; 2 had generalized anasarca. Three of the younger patients had persistent diarrhea with poor digestion of food early in the disease. In mild cases, nutrition was not impaired, but in moderate to severe cases, pallor and wasting were marked. Hepatomegaly and ascites seemed to be associated with the younger, more severely ill children and disappeared within a year in each instance. The liver was not tender and was smooth. Associated enlargement of the spleen was noted in only 1 case. Two had migrating nodules, most of which disappeared spontaneously within 1 or 2 months. In 1, masses appeared in the abdominal cavity, the subcutaneous tissues of the sole of the right foot, the scalp, the abdominal wall, and the right retro-orbital region, causing marked exophthalmos and hemorrhage of the retina; involvement of the intracranial region produced a Jacksonian type of convulsion which left a slight weakness of the left extremities and a widening of the sutures, as demonstrated by x-rays of the skull. In 1, a mass appeared in the left breast muscle. One patient had a persistent, severe headache; trephination disclosed multiple cysts which contained thick yellow pus in the right parieto-occipital region (see Table I).

LABORATORY DATA

The red blood cell counts varied from 3.5 million to 4.4 million per cubic millimeter, with hemoglobin levels ranging from 8.3 Gm. to 14.0 Gm. per 100 c.c. The hemoglobin level of the severely ill patients was reduced during the acute stage and was elevated again as the patient improved. The white blood cell count varied from 10.4 thousand to 41.8 thousand per cubic millimeter, with a mean of 18.8 thousand per cubic millimeter; of these 11 to 52 per cent, with a mean of 35 per cent, were eosinophils. The eosinophil count ranged between 1.3 and 10.8 thousand per cubic millimeter, with a mean of 6,600 per cubic millimeter. Study of the bone marrow revealed an eosinophilic hyperplasia with 70 to 80 per cent mature forms. Biopsy of a subcutaneous nodule from the left hypochondrial region in 1 case showed an eosinophilic granuloma. Thymol turbidity was 18.6 units in 2 cases and 15.2 units in 1 case. Readings of cephalin flocculation were two plus in 24 hours and three plus in 48 hours in 3 cases. Serum protein levels ranged from 6.9 to 10.2 Gm. per 100 c.c. In mild cases the albumin and globulin ratio was not reversed, but in moderate to severe cases the A/G ratio was usually reversed; in the most severe case the A/G ratio was 2.75:7.45 or 0.37:1 during the most acute phase, returning almost to normal 10 months later. Paper electrophoresis revealed a marked increase in the gamma globulin fraction (see Fig. 5). In the pleural fluid and pus from 2 patients (Cases 3 and 8) 85 to 90 per cent of the cells were eosinophils; in one (Case 1) 90 per cent of the cells in the peritoneal fluid were eosinophils and in another (Case 2) 89 per cent of the cells in the pericardial fluid were eosinophils. Skin tests for paragonimiasis were positive in all 8 patients. Tuberculin tests with 500× and 2,000× old tuberculin were all negative except in 1 child (Case 4) who also had tuberculous meningitis. Eggs of *Paragonimus westermani* were demonstrated in 4 of the 8 patients, 3 having ova in the sputum and 1 in pus from a brain cyst; in 1 of these the stool was also positive for ova. Skin tests for coccidioidomycosis, blastomycosis, histoplasmosis, and toxoplasmosis were all negative. Urinalyses and levels of serum calcium, phosphorus, and bilirubin were within normal limits. The prothrombin time was not increased in 3 children with hepatomegaly. Serologic tests for syphilis were all negative. The erythrocyte sedimentation rate in a mild case was 10 mm. in one hour (Wintrobe, uncorrected); in one (Case 1) it was 56 mm. in one hour uncorrected. Lumbar punctures were performed on 1 patient (Case 4) and revealed spinal fluid under an increased pressure of 480 mm. of water.

Table I. Clinical findings in childhood paragonimiasis

Cases (all boys)	*Age*	*Date of measles*	*No. of crayfish ingested*	*Incubation period and first symptoms*	*Date of first visit*	*Chief complaint at the first visit*	*General appearance, nutrition at the first visit*
1 (K. H. S.)	2 Years 10 Months	April 5, 1958	5	30 days with cough, fever, and convulsion	Sept. 29, 1958	Abdominal distention, cough, dyspnea, fever, and edema	Pale, poor nutrition
2 (K. N. H.)	3 Years 2 Months	Aug. 11, 1958	5	20 days with diarrhea, fever, and convulsion	Nov. 6, 1958	Cough, dyspnea, fever and generalized edema	Pale, poor nutrition
3 (L. I. K.)	2 Years 11 Months	May 5, 1958	5	25 days with fever and convulsion	Nov. 28, 1958	Fever, cough, and diarrhea	Pale, poor nutrition
4 (K. Y. C.)	7 Years 5 Months	April 15, 1953	5	30 days with cough and fever	March 13, 1959	Headache, fatigability, and malaise	Pale, fair nutrition
5 (K. M. H.)	8 Years 1 Month	April 8, 1958	3	30 days with cough and fever	May 25, 1959	Cough, occasional headache, and vomiting	Normal, good nutrition
6 (K. K. H.)	5 Years 6 Months	April 11, 1958	3	Not definite	June 5, 1959	Cough and sputum	Normal, good nutrition
7 (B. T. J.)	5 Years 7 Months	Aug. 21, 1958	5	Not definite but not well after measles	July 14, 1959	Cough and night sweating	Normal, good nutrition
8 (I. Y. B.)	11 Years 1 Month	March 23, 1957	5	Not well after measles, cough	Sept. 25, 1959	Cough, dyspnea, and irregular fever	Pale, good nutrition

The cell count was 333 per cubic millimeter with 55 per cent of eosinophils; the cerebrospinal fluid showed an increased protein level of 324 mg. per 100 c.c. and a decreased sugar level of 16.7 mg. per 100 c.c. The fluid was slightly xanthochromic and hazy. The laboratory data on one (Case 1), considered to be one of the most severely ill patients, are shown in Table III. Chest roentgenograms revealed blotchy, ill-defined pulmonary densities or fluffy, ill-defined pneumonic consolidations with or without pleural effusion on one or both sides, at times accompanied by interlobar pleurisy, particularly on the right side. Skull x-rays of that child revealed widening of the coronary and sagittal sutures suggesting increased intracranial pressure. Skull x-rays of another (Case 4) showed amorphous calcification in the right parietal area; a ventriculogram revealed dilatation of the lateral and the third ventricles (Fig. 6). Two patients (Cases 1 and 2) had had pet dogs about one year prior to the onset of the disease; samples of soil gathered from where the dogs habitually defecated did not reveal ova of *T. canis*.

Hepatomegaly and body fluids accumulated at the first visit	*Migrating masses*	*X-ray findings*	*Complications and sequelae up to October, 1959*
8 cm. below the right costal margin with pleural and peritoneal effusion	Present	The cardiac shadow is grossly enlarged. Fluffy, ill-defined increased density involving both lung fields with small bilateral pleural effusion. Skull x-rays show widening of the coronary and sagittal sutures suggestive of increased intracranial pressure	Mild hemiparesis in the left extremities and occasional twitching of the jaw and left arm
5 cm. below the right costal margin with pericardial effusion	Absent	Small pleural effusion bilaterally associated with marked pericardial effusion	None
5 cm. below the right costal margin with ascites and pleural effusion	Absent	Blotchy, ill-defined increased density involving both lung fields. Pleural effusion on the right and minimum on the left. Interlobar pleurisy in the right minor fissure. Skull x-ray is negative	Occasional generalized convulsion without signs of increased intracranial pressure
None	Absent	Increased densities in both lung bases with cystic areas in the left base and right middle lung fields. Skull x-ray shows calcification in the right parietal area. Ventriculogram shows both lateral and third ventricles are dilated; fourth ventricle is not visualized	Tuberculous meningitis, blindness with optic atrophy, and moderate mental retardation
Pleural effusion	Absent	Fluffy, ill-defined areas of density in both lung fields more marked in the middle lung fields bilaterally. Mild pleurisy in the left, interlobar pleurisy in the right. Skull x-ray is negative	Frequent attacks of severe headaches especially in the morning
None clinically	Absent	Pneumonic consolidation in the right upper and lower lung fields with small pleural effusion and interlobar pleurisy in the right minor fissure. Skull x-ray is negative	None
None	Absent	Fluffy, ill-defined pneumonic consolidation involving both infraclavicular areas and the left middle and lower fields. Right hilar shadow is also enlarged	None
Massive pyothorax	Present	Massive dense homogenous clouding of the right hemithorax with displacement of the trachea, heart, and mediastinum to the left, suggesting massive pleural effusion	None

COURSE

In considering the course of the disease, it is desirable to divide the patients into four groups: (1) those who had demonstrated lesions only in the lungs, (2) those who had lesions in the lungs and such pleural involvement as effusion or empyema, (3) those who had ascites, hepatomegaly, or pericardial effusion, in addition to the findings of the first 2 groups, and (4) those who had neurologic manifestations, with or without the lesions in the first 3 groups.

Group 1. In this group was a boy 5 years and 7 months of age (Case 7). He came to the hospital with the chief complaint of mild fever, cough, and night sweats. He had done poorly after a bout of measles 11 months prior to his first visit to this hospital. A diagnosis of pulmonary tuberculosis had been made at a private clinic, and he had received antituberculosis therapy. An x-ray of the chest showed pneumonic consolidations in both infraclavicular areas and the left middle and lower fields and an enlarged right hilar shadow (Fig. 1). He was admitted to this hospital for evaluation and

Table II. Laboratory data on cases of paragonimiasis in children

Case no.	*R.B.C. (million)*	*W.B.C. (thousand)*	*Hemoglobin (Gm. 100 c.c.)*	*Segmented neutrophils (%)*	*Stab neutrophils (%)*	*Lymphocytes (%)*	*Monocytes (%)*	*Eosinophils (%)*	*Basophils (%)*	*Eosinophils per cmm. (thousand)*	*Platelet (thousand)*	*Tuberculin skin test*	*Paragonimiasis skin test*	*Coccidioidomycosis skin test*	*Histoplasmosis skin test*	*Blastomycosis skin test*
1	3.5	19.5	8.3	41	1	29	3	26	0	3.3	318	Negative	Positive	Negative	Negative	Negative
2	4.3	16.4	14	29	2	33	4	32	0	5.6	272	Negative	Positive	Negative	Negative	Negative
3	4.4	22.0	12	16	0	32	0	52	0	10.8	278	Negative	Positive	Negative	Negative	Negative
4	3.8	10.4	12	49	3	31	6	11	0	1.3	265	Positive	Positive	Negative	Negative	Negative
5	4.2	17.2	14	32	1	34	1	32	0	2.8	256	Negative	Positive	Negative	Negative	Negative
6	4.1	19.4	13.5	18	0	34	8	40	0	8.5	280	Negative	Positive	Negative	Negative	Negative
7	3.7	10.6	12	36	0	45	2	17	0	1.8	—	Negative	Positive	Negative	Negative	Negative
8	4.0	11.3	13	20	0	43	4	33	0	2.4	—	Negative	Positive	Negative	Negative	Negative

treatment with his illness tentatively diagnosed as pulmonary tuberculosis. His family had never owned dogs or cats. A history of pica and dirt-eating was not obtained. Blood counts of both parents showed no eosinophilia. On physical examination he appeared well nourished, well developed, and in good health. Laboratory data (Table II) included repeated tuberculin tests that were all negative; the stool was positive for ova of *P. westermani* and showed no ova of other parasites. A skin test for paragonimiasis was positive; the sputum was also positive for *P. westermani* ova. His history revealed that he had once ingested 5 raw crayfish after squeezing and mashing them; there was no other known exposure to paragonimiasis. Thirty milligrams of emetine hydrocholoride was administered intramuscularly for 10 days along with 3.0 Gm. of sulfadiazine per day; subsequently, 0.4 Gm. of chloroquine diphosphate given orally daily for 10 days was added to the above therapy. The sputum and stool remained negative for *P. westermani* ova for 3 months, and there was marked improvement in the x-ray findings and the clinical symptoms.

Group 2. There were 3 patients in this

Toxoplasmosis skin test	*Specimens for eggs of P. westermani*	*Specific findings of body fluids*	*Total protein with A/G*	*Gamma globulin Gm. per dl.*	*Thymol turbidity (unit)*	*Eggs of parasite in the stool*	*Findings in bone-marrow*	*Erythrocyte sedimentation rate per hour*	*Serologic test for syphilis*
Negative	Negative	Peritoneal fluid cell count 7,776; 4% neutrophils, 6% lymphocytes, 90% eosinophils	10.2 A. 2.75 G. 7.45	4.82	18.6	Negative	Eosinophilic hyperplasia	56 mm.	Negative
Negative	Negative	Pericardial fluid cell count 224,000 with 89% eosinophils	6.9 A. 2.9 G. 4.0	2.99	15.2	Negative	Eosinophilic hyperplasia	51 mm.	Negative
Negative	Negative	Pleural effusion cell count 926; 15% lymphocytes, 85% eosinophils	7.1 A. 2.8 G. 4.3	— (Not done)	18.6	Negative	—	45 mm.	Negative
Negative	Pus from brain cyst	Cerebrospinal fluid cell count 333; 3% neutrophils, 42% lymphocytes, 55% eosinophils	7.4 A. 3.5 G. 3.9	—	—	Ascaris	—	18 mm.	Negative
Negative	Sputum	—	7.6 A. 4.2 G. 3.4	—	—	Negative	—	14 mm.	Negative
Negative	Sputum	—	—	—	—	Negative	—	10 mm.	Negative
Negative	Sputum and stool	—	7.3 A. 4.0 G. 3.3	—	—	Negative	—	16 mm.	Negative
Negative	Negative	Pleural pus cell count 8,500 with 90% eosinophils	6.07 A. 3.23 G. 2.84	—	—	Ascaris	—	20 mm.	Negative

group (Cases 5, 6, and 8). A boy 8 years old (Case 5) came to the hospital with the chief complaint of cough, occasional vomiting, and severe headaches. These symptoms first started about 1 month after a bout of measles 13 months prior to his first visit to our hospital. In another hospital he had been thought to have pulmonary tuberculosis associated with a left pleural effusion and had been treated for 2 months without improvement. On physical examination, he was fairly well nourished and well developed with occasional dry râles throughout the lung fields; the left lower chest was somewhat dull to percussion. The liver and spleen were not palpable. Laboratory data on this case are shown in Tables I and II. Repeated skin tests for tuberculosis were all negative; the skin test for paragonimiasis was positive, and the sputum contained *P. westermani* ova. A chest x-ray is shown in Fig. 2. After treatment with emetine hydrochloride, sulfadiazine, and chloroquine for 1 month, repeated sputum examinations for *P. westermani* ova were negative for 4 months, although the patient complained of an occasional severe headache in the morning. There was no evidence of increased intracranial

Table III. Laboratory data on Case 1*

Date examined	*Sept. 30, 1958*	*Oct. 4 and 5 1958*	*Oct. 11, 1958*	*Oct. 17, 1958*	*Oct. 19, 1958*	*Oct. 21, 1958*	*Oct. 23, 1958*	*Oct. 24, 1958*	*Nov. 6, 1958*	*Nov. 14, 1958*	*Dec. 2, 1958*	*Dec. 10, 1958*	*Dec. 15, 1958*	*Feb. 2, 1959*	*July 22, 1959*
R.B.C. (million)	3.5		4.3				Delta-			3.6	3.0	3.2		4.0	4.0
Hb. (Gm. per 100 ml.)	8.3	250 c.c.	12.5				cortone		11.5	10.5	10.0	11.0	11.0	12.0	11.5
W.B.C. (1,000)	19.5	each,	18.5	10.2	46.5	57.5	30 mg.	19.1	22.6	21.4	9.4	11.9	15.8	31.7	14.6
Segmented neutrophils (%)	41	total of 500	20	31	24	15	daily for 7 days;	56	47	29	21	20	26	25	38
Stab neutrophils (%)	1	c.c.	0	1	0	0	then	3	3	0	1	0	2	0	0
Lymphocytes (%)	29	blood	43	38	29	28	gradually	31	36	40	37	33	41	33	31
Eosinophils (%)	26	trans-	36	28	46	57	stopped	8	12	27	40	44	28	41	29
Monocytes (%)	3	fusion	1	2	1	0		2	2	4	1	3	3	1	2
Platelet (1,000)	318					306					292				
Eosinophils per cmm. (1,000)	3.3		7.6					1.2			3.6				
Stool for parasite ova	Negative		Negative					Negative				Negative			Positive in ascaris
Total protein	8.6		10.2					9.4				8.5			7.35
albumin	2.25		2.75					2.85				3.0			3.9
globulin (Gm. per 100 ml.)	6.35		7.45					6.55				5.5			3.45
Gamma globin (Gm. per 100 ml.)				4.82						3.74					
Skin test for tuberculosis with 2,000×	Negative		Negative									Negative			Negative
500×	Negative			Negative								Negative			Negative
Skin test for *P. westermani*															Positive
Sputum for acid-fast bacilli*	Negative		Negative									Negative			Negative
Sputum for *P. westermani* ova (including gastric washing)															Negative
Erythrocyte sedimentation rate (mm. per hr.)	56											58		32	28
Soil for *Toxocara canis* ova				Negative											
Biopsy of subcutaneous nodule												Eosinophilic granu-loma			

*A part of the laboratory data on this case shown in Table II is omitted to avoid duplication.

pressure or of any abnormalities on a skull x-ray.

A 5½-year-old boy (Case 6) did not have any serious subjective symptoms except for an occasional cough with a small amount of white sputum. Two brothers (Cases 5 and 6) were checked at the same time because of a suspicion of pulmonary tuberculosis in one (Case 5). It was found that the brother had marked eosinophilia with leukocytosis, a positive skin test for paragonimiasis, and a negative skin test for tuberculosis, mycotic infections, and toxoplasmosis. Ova of *P. westermani* were found in the sputum; laboratory data and chest x-ray findings are shown in Tables I and II. These siblings (Cases 5 and 6) were found to have eaten 3 crayfish each for the treatment of measles at the same time; no other exposure to paragonimiasis was revealed from the history. After treatment with emetine hydrochloride, sulfadiazine, and chloroquine for 1 month, ova of *P. westermani* disappeared for 4 months, with marked improvement in the chest x-ray findings.

An 11-year-old boy (Case 8) came to the hospital with the chief complaint of a nonproductive cough, severe dyspnea, and irregular fever for 7 months. He had been treated by a local physician for a right pleural empyema presumed to be tuberculosis. On physical examination he was fairly well nourished but pale. He was extremely dyspneic; the right side of the chest bulged markedly. Breath sounds were absent on auscultation and there was complete dullness to percussion over the entire right chest. Otherwise the physical examination revealed nothing unusual. After admission, repeated thoracenteses performed daily for 1 week produced a total of 5,600 c.c. of pus, until no more pus was obtained. Repeated cultures for pyogenic organisms and acid-fast bacilli were all negative, and repeated examinations for *P. westermani* ova were also negative. A differential count of the pus showed a 90 per cent eosinophilia. Skin tests for tuberculosis, mycotic infections, and toxoplasmosis were all negative; the skin test for paragonimiasis was positive. Chest x-rays and other laboratory findings are shown in Fig. 3 and Tables I and II. His history revealed that he had ingested 5 crayfish at the time he had measles 2½ years prior to this admission; there was no other known exposure to paragonimiasis. After treatment with emetine hydrochloride, sulfadiazine, chloroquine, and repeated thoracenteses over a 50-day period, no more pus accumulated and there was marked clinical improvement. During hospitalization a mass in the left pectoralis major muscle about 3.0 by 1.5 cm. in size suddenly appeared; biopsy of this

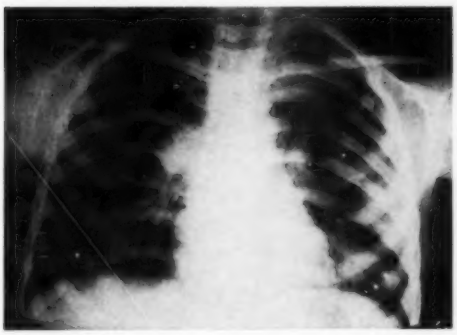

Fig. 1. Chest x-ray of B. T. J. (Case 7) showing fluffy, ill-defined pneumonic consolidations involving both infraclavicular areas and the left middle and lower fields. An enlarged right hilar shadow can also be seen.

Fig. 2. Chest x-ray of K. M. H. (Case 5) showing fluffy, increased areas of density in both lung fields more marked in the middle lung fields bilaterally. There is mild pleurisy on the left and interlobar pleurisy on the right.

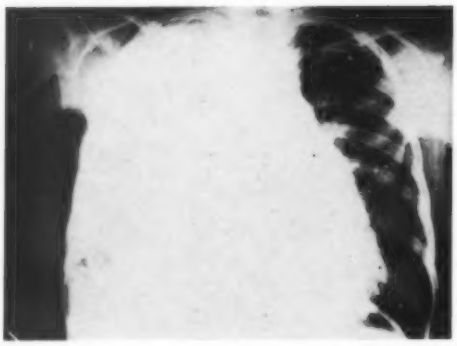

Fig. 3. Chest x-ray of I. Y. B. (Case 8). Note the massive dense homogenous clouding of the right hemithorax with displacement of the trachea, heart, and mediastinum to the left, suggesting massive pleural effusion.

Fig. 4. Chest x-ray of K. N. H. (Case 2) showing small pleural effusion bilaterally associated with marked pericardial effusion.

mass revealed myositis with marked eosinophilic infiltration. No ova or adult forms of *P. westermani* were found in this biopsy.

Group 3. In this group were 2 patients (Cases 2 and 3). A boy 3 years old (Case 3) had had persistent diarrhea and cough with wheezing following measles; 20 days later there were generalized convulsions and moderate fever accompanying the above symptoms. The convulsions were followed by dyspnea and generalized edema. He had been admitted to another hospital and treated on the basis of acute glomerulonephritis for 2 months, during which time the symptoms became progressively worse. When he came to our hospital, he was markedly edematous, pale, and in acute distress. The left anterior chest was dull to percussion and the precordial dullness markedly increased; heart sounds were distant on auscultation. The abdomen was diffusely distended and the liver was palpable 5 cm. below the right costal margin; there was intraabdominal fluid and extreme pitting edema in both legs. An x-ray of the chest is shown in Fig. 4. Pericardial paracentesis was performed; 89 per cent of the cells in the pericardial fluid were eosinophils. Repeated urinalyses, blood pressure determinations, and nonprotein nitrogen levels were all within normal limits. Repeated blood counts showed persistent leukocytosis with marked eosinophilia. Aspiration of the bone marrow revealed eosinophilic hyperplasia with 70 per cent mature forms. No arrest of maturation or malignant tumor cells were seen. After one aspiration of 35 c.c. of pericardial effusion, the edema gradually disappeared and the liver returned to normal size within 10 days of admission. Even though the symptoms were markedly improved after discharge from the hospital, persistent mild wheezing and cough continued for many months. After 3 other patients (Cases 5, 6, and 7), were found to have paragonimiasis, a more careful history was obtained and it was found that he had ingested 5 crayfish for the treatment of measles. This fact and the results of laboratory studies are shown in Tables I and II. A skin test for paragonimiasis was positive. Thymol turbidity was 15.2 units. However, ova of *P. westermani* were not demonstrated on repeated examinations of sputum, stool, and gastric washings. Treatment with emetine hydrochloride, sulfadiazine, and chloroquine was given for 1 month without much change.

A boy 2 years and 11 months old (Case 3) came to our hospital with the chief complaint of fever, cough, and persistent diar-

rhea. He had not been well since he had had measles about 7 months prior to the first visit to our hospital. He had had a few generalized convulsions with high fever 25 days after having measles, and had been admitted to another hospital where he was treated for what was thought to be pulmonary tuberculosis with pleural effusion and tuberculous peritonitis for 2 months but without effect. On physical examination he was fairly well developed but pale, poorly nourished, and in acute distress. Several cervical lymph nodes were palpable without tenderness; occasional dry râles were heard throughout the lung fields; sounds of breathing were weak in the right base, where the percussion note was dull, and there was crepitation. The abdomen was diffusely distended, there was ascites, and the liver was felt 5 cm. below the right costal margin; no mass was palpable in the abdomen. Pleural fluid obtained by thoracentesis showed 85 per cent eosinophils but no parasitic ova. Chest x-ray and laboratory findings are shown in Tables I and II. Thymol turbidity was 18.6 units; cephalin flocculation was 2 plus in 24 hours and 3 plus in 48 hours. This had been considered to be a case of eosinophilia syndrome with hepatomegaly until 3 patients (Cases 5, 6, and 7) were demonstrated to have paragonimiasis following ingestion of raw crayfish for the treatment of measles. For several months he suffered from occasional generalized convulsions without showing any evidence of increased intracranial pressure or abnormal calcification as seen by x-ray of the skull or by funduscopic examination. After identification of the disease in these 3 other patients, additional history revealed that he had ingested 5 crayfish when he had measles. A skin test for paragonimiasis was positive; a tuberculin test was negative. Skin tests for mycotic infections and toxoplasmosis were also negative. Examinations of the sputum and stool were negative for *P. westermani* ova. After the administration of emetine hydrochloride, sulfadiazine, and chloroquine for 1 month, the clinical symptoms and x-ray findings of the chest were markedly improved.

Group 4. In this group there were 2 patients (Cases 1 and 7). One (Case 1) was a boy 2 years and 10 months old; he was the first with this syndrome that I encountered. He came to our clinic with the chief complaint of cough, fever, and abdominal distention with generalized edema. Following measles, he had had cough and malaise for 1 month and a generalized convulsion with high fever. He had been admitted to another hospital where a diagnosis was made of pulmonary tuberculosis activated by measles. On physical examination he was pale and malnourished. Several anterior and posterior cervical lymph nodes were palpable. Mixed dry and moist râles were heard throughout the lung fields; in the right base the sounds of breathing were diminished, and the percussion note was dull. The pulse rate was 130. His weight was 26 pounds. The abdomen was diffusely distended, the liver was down 8 cm. below the right costal margin, the spleen was just palpable, and there was abdominal fluctuation. There was a hard, round, smooth mass about 4 by 5 cm. in the periumbilical region. Peritoneal fluid obtained by paracentesis, performed to relieve severe dyspnea, showed 7,776 cells per cubic millimeter with 90 per cent eosinophils. Repeated blood counts revealed a persistent leukocytosis with marked eosinophilia (Table III). Total proteins were elevated to 10.2 Gm. per 100 c.c. with an albumin level of 2.75 Gm. per 100 c.c. and a globulin level of 7.45 Gm. per 100 c.c. Paper electrophoresis showed a marked globulin elevation, especially of gamma globulin (Fig. 5). Repeated tuberculin tests with 2,000× and 500× dilutions were all negative; this was interpreted as being an anergic tuberculous condition following measles. Digitalization was performed and he was given antituberculosis medication throughout the first admission for 1 month, although the possibility of his having visceral larva migrans was considered. By the time he was discharged the generalized edema had completely disappeared, moderate ascites and hepatomegaly persisted, and

the mass in the periumbilical region had almost disappeared. After discharge, a subcutaneous nodule appeared in the sole of the right foot and another one in the lower inner aspect of the right thigh, with swelling of several inguinal lymph nodes; a third nodule appeared in the left hypochondrial region and then several appeared in the scalp. The nodules were tender to palpation and had some redness; they usually disappeared spontaneously within 1 month. Two months after the first discharge the patient entered the hospital for re-evaluation of the disease. A biopsy of the nodule in the left hypochondrial region was performed and was reported to be an eosinophilic granuloma; no foreign bodies, larva, or ova of parasites were seen; cultures for fungus and bacteria were all negative. Biopsies of the lymph nodes from the right inguinal and right axillary regions showed nothing remarkable. During the second admission, tuberculin tests were again negative. The total protein, particularly the gamma globulin level, was a little lower than during the first admission. The third admission, on July 22, 1959, 8 months after the second admission, was made in order to evaluate some new phenomena, namely, exophthalmos in the right eye with marked swelling of the right upper lid and a weakness of the left arm and leg following several episodes of twitching in the left arm and jaw. An x-ray of the skull showed widening of the coronary and sagittal sutures and suggested increased intracranial pressure. An ophthalmoscopic examination revealed choked disks on both sides and a slight retinal hemorrhage on the right side. The neurosurgeon recommended a ventriculogram, but the parents, hoping that the condition would subside spontaneously as had the subcutaneous masses, did not permit the study. An attempt to perform a biopsy of the nodule in the right upper lid failed because the nodule disappeared during the procedure. By this time, fortunately, some of the instances of eosinophilia syndrome in this age group were clearing and were proving to be cases of paragonimiasis. A review of his past history disclosed that he had ingested 5 crayfish for the treatment of measles earlier. A skin test for paragonimiasis was positive; a skin test for tuberculosis was again negative, and skin tests for 3 mycotic infections and for toxoplasmosis were all negative. Although ova of *P. westermani* were not found in the sputum, the diagnosis of paragonimiasis seemed quite certain.

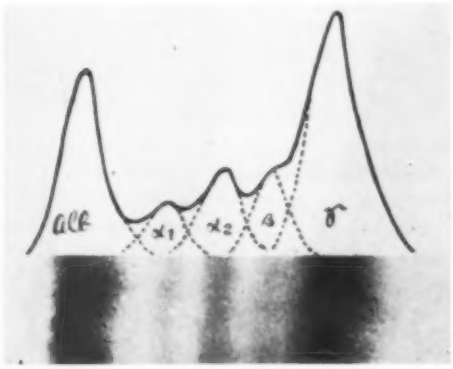

Fig. 3. Paper electrophoresis of K. H. S. (Case 1) showing increased globulin fraction, particularly the gamma globulin level. Albumin is 2.72 Gm. per 100 ml.; alpha$_1$ globulin, 0.61 Gm. per 100 ml.; alpha$_2$ globulin, 1.14 Gm. per 100 ml.; beta globulin, 1.0 Gm.; and gamma globulin, 4.82 Gm. per 100 ml. Total protein is 10.29 Gm. per 100 ml., with an A/G ratio of 0.36.

A 7½-year-old boy (Case 7) came to our hospital with the chief complaint of persistent severe headache, malaise, and easy fatigability for 2 months. After having measles, he was said to have had pulmonary tuberculosis for about 6 years. One month prior to this admission it was thought, at a private clinic, that he had tuberculous meningitis and he was treated there for 1 month. On examination he was pale but fairly well nourished. A left homonymous field defect and slight weakness of the left extremities were noted; otherwise, no abnormalities were found. A tuberculin skin test and a skin test for paragonimiasis were positive, but tests for mycotic infections and toxoplasmosis were all negative. Laboratory data and x-ray findings are shown in Tables I and II. On April 5, 1959, a craniotomy in

the right parieto-occipital region was performed. About 2 cm. deep in the cerebral cortex, a cyst wall was encountered. The cyst was separated easily from the surrounding cerebral tissue because of the calcified thick wall and was removed. It was approximately 5 cm. in diameter and contained thick pus. Three other small cysts were also removed at the same time. On cut section, the cyst was filled with a gray-white, friable material; the wall of the capsule measured 0.5 cm. in thickness. Microscopic examination showed the cystic wall to consist of dense, hyalinized, fibrous tissue. The cystic space was filled with an eosinophilic amorphous material. There were scattered ova identified as *P. westermani;* no adult form was found. After removal of the cysts from the brain, the headaches did not subside, and internal strabismus of the left eye was noticed 15 days after craniotomy. He was readmitted for evaluation of this new condition. A ventriculogram showed symmetrical dilatation of the third and lateral ventricles with a large amount of air in the right parieto-occipital region where the cysts had been excised. The aquaeductus and the fourth ventricle were not visualized (Fig. 6). Perhaps by error, a culture for acid-fast bacilli made on a previous admission had been reported as positive, and so antituberculosis treatment was reinstituted with a working diagnosis of cerebral paragonimiasis and tuberculous meningitis. Three months later, on a second admission, he no longer complained of headaches, but developed optic nerve atrophy with blindness and moderate mental retardation. He had ingested 5 crayfish for the treatment of measles about 6 years ago; otherwise there was nothing in his history to indicate paragonimiasis.

Fig. 6. Ventriculogram of K. Y. C. (Case 7). This lateral view shows uniformly dilated lateral ventricles and third ventricle without evidence of displacement or filling defect. Fourth ventricle is not visualized.

DISCUSSION

Among the causes of eosinophilia is helminthiasis. Cases with chronic eosinophilia of uncertain cause, such as tropical eosinophilia, familial eosinophilia, Löffler's syndrome, eosinophilic pseudoleukemia, and various others, have been studied for many years. A newly recognized syndrome with chronic eosinophilia as a prominent feature has appeared in infants and young children. Five recent reports[1, 2, 3, 7, 8] have described, in young children, a chronic extreme eosinophilia accompanied by eosinophilic granulomatous lesions in an enlarged liver, together with some degree of pulmonary infiltration, fever, cough, and hyperglobulinemia.

Perlingiero and György[7] have reported such a case in the presence of infestation of Ascaris in the gastrointestinal tract. Although no nematode larvae or other parasites or organisms were found in the lesions of the liver, they mentioned the possibility that the hepatic lesions may have been on the basis of an allergic response to Ascaris toxin. Zuelzer and Apt[8] reported 8 such cases, the largest single group reported to date. No definite etiologic agent could be proved in any of their cases, but the hepatic lesions that were described in 4 and the general picture of the others are all suggestive of visceral larva migrans. Mercer and colleagues[1] reported a case with typical findings of this syndrome and were the first to

identify an etiologic agent in the hepatic lesions; a nematode larva was found which they identified as *A. lumbricoides*. Behrer[2] described another case with all the cardinal features of this syndrome and in which, for the second time, the larva of *A. lumbricoides* was found in the liver as the etiologic agent. Beaver[3] and his group reported 3 cases. In one of these, they discovered the larva of *T. canis*. They postulated that the syndrome is probably caused by nematode larvae migrations through the liver and other viscera.

The first 3 patients whom I have seen (Cases 1, 2, and 3) had symptoms so similar to those of visceral larva migrans that vigorous efforts were made to try to find larva of *T. canis*, but this was not possible without getting a liver biopsy for which the parents obstinately refused to grant permission. Then one patient (Case 1) unexpectedly developed focal epilepsy with exophthalmos in the right eye and with x-ray evidence of increased intracranial pressure. Another (Case 4) was found to have cerebral paragonimiasis, in which ova of *P. westermani* were identified from the pus of one of the cysts obtained from the right parieto-occipital region of the brain; he also had tuberculous meningitis. A little later, 2 siblings (Cases 5 and 6) came to our clinic with pulmonic infiltrations, pleural effusion, and marked eosinophilia. They were found to have paragonimiasis by demonstrating ova of *P. westermani* in their sputum. A little later, one (Case 7) was admitted with a possible diagnosis of pulmonary tuberculosis, but a final diagnosis of paragonimiasis was made when ova of *P. westermani* were demonstrated in the sputum and stool; tuberculin skin tests were repeatedly negative. Incidentally, when 4 patients (Cases 4, 5, 6, and 7) were all found to have ingested crayfish (*Astacus similis*, Fig. 7) for the treatment of measles, the past histories of the former 3 were rechecked, and they too were found to have ingested 5 raw crayfish, each at the time they had measles. Skin tests for paragonimiasis performed in the former 3 patients were also found to be positive even though the ova of *P. westermani* were not demonstrated in all three. Later I found that this custom of taking raw crayfish for the treatment of measles is prevalent throughout Korea, in both cities and rural areas. For the severe forms of measles it is believed by the many Korean people who use ancient herb medicines to be particularly efficacious. Commonly, the raw crayfish are mashed and strained, and the juice given for medication.

Paragonimiasis is not uncommon among adults in Korea. According to Walton and Chyu,[9] the most highly endemic area in Korea is Cheju Do, where 47 per cent of all individuals are infected. The lowest incidence is in Kyongi Do, where the rate is 3 per cent. Nakagawa[10] first reported in 1917 that *Potamon de haanii White, Potamon rathbuni de Man*, and *Eriocheir sinensis* were the second intermediate hosts in Taiwan, and Faust[11] in 1928 agreed with the report. Miyairi[12] in 1917 first identified crayfish as being the major second intermediate host of *P. westermani* in Korea. He also stated that the species of crabs which served as second intermediate hosts differed from country to country and from district to district. It is also well known that *Semisulcospira libertina* Gould and *Semisulcospira libertina extensa* (snail) are the first intermediate host in which the miracidia of Paragonimus live.[13] Miyakawa[14] reported that the infection rate of crayfish in Kaechun district, Pyongnam, Korea, by metacercaria in 1918 was 98.2 per cent; 84.8 per cent lived in muscles, 12.0 per cent in gills, and 1.4 per cent in the liver. Chyu[15] said that metacercaria found in the gills of crayfish are matured completely and at room temperature die in 4 hours after leaving; when metacercaria are kept in the refrigerator, they can survive for more than 2 days. They are difficult to demonstrate in dead crabs. In a thickly infected district, almost 100 per cent of crabs contain metacercaria, while in a less infected district there may be only 2 to 3 per cent. In Korea there is an average infectivity of 20 to 50 per cent. According to Yokogawa,[16] metacercaria probably can survive for several years in

Fig. 7. *Astacus similis* (a crayfish), one of the second intermediate hosts of *Paragonimus westermani.*

living crabs and for 10 to 30 days in cool water. When raw crabs which may contain numerous metacercaria are ingested, the possibility of massive infection is greatly increased. An ectopic infection occurs when organs other than the lungs are involved. Ectopic infections by *P. westermani* have been described by Chyu,[17] Mitsuno,[18, 19] Yokogawa,[20] Ji,[21] Shin,[22] Busch and coworkers,[23] and recently by Lee and associates,[24] who dealt mostly with cerebral paragonimiasis. According to Mitsuno[19] and Lee,[24] younger patients have a greater tendency toward cerebral paragonimiasis. Peritoneal,[25] subcutaneous,[26] and retro-orbital paragonimiasis[27] have also been reported as ectopic paragonimiasis. Chyu[15] investigated paragonimiasis in Chunnam, Korea, and found 12 cases of ectopic infection in 65 cases of paragonimiasis, among which 7 were cases of cerebral paragonimiasis. The rate of morbidity as determined by the finding of *P. westermani* ova in the sputum increased with age; below 10 years of age, the morbidity rate was 10 per cent, but at 60 years of age it became 50 per cent. The adult worm, however, may survive for 15 to 20 years in the terminal host. The possibility of a reinfection is also to be considered in the older age group. In order to confirm a diagnosis of paragonimiasis, ova of *P. westermani* should be demonstrated in the sputum or in other body fluids or tissues, but since ova are not always demonstrable, other laboratory procedures also are essential. Antigen for skin testing for paragonimiasis was first elaborated in 1939 by Tominaga[28] and a purified antigen was developed for intradermal testing for *P. westermani* by Sadun[29] which in a preliminary survey, proved to be a reliable tool for the epidemiologic investigation of paragonimiasis. It was said that all of the persons with proved paragonimiasis gave positive reactions and that less than 1 per cent of the trematode-free control group reacted positively. Some positive reactions with Paragonimus antigen were observed in people with other trematode infections, although the reactions to the homologous antigens were generally much greater. X-rays of the chest of those whose illness is uncertain and x-rays of the skull of those who have central nervous system symptoms are essential for diagnosis, but pulmonary tuberculosis, histoplasmosis, blastomycosis, and coccidioidomycosis and toxoplasmosis of the brain should be ruled out by their respective skin tests. Eosinophilia in paragonimiasis usually ranges from 10 to 20 per cent, but may be as high as 50 per cent;[17] in the younger age group, marked eosinophilia indicates a severe, active phase of the disease, and lesser eosinophilia is seen in the more chronic cases. Hyperglobulinemia also seems to be related to the severity of the disease. In the more active phase, the globulin level is likely to be elevated. It returns to normal when the disease becomes chronic (Cases 1 and 2).

The prevention of paragonimiasis is urgently needed and could be achieved easily through adequate public health education. Such a program would reveal the danger of ingesting raw crayfish for the treatment of measles or for any other purpose. Meas-

ures can be taken to eliminate snails, crayfish, and crabs from rivers and streams. No effective, specific treatment for human infection has been found. Emetine hydrochloride, antimony preparations, sulfadiazine, gentian violet, chloroquine, and pyribenzamine have all been used with indifferent success. A combination of sulfadiazine and emetine hydrochloride is said to be effective in reducing the number of *P. westermani* ova in the sputum. Yokogawa and Ro[30] reported that the combination of prontosil with emetine hydrochloride used experimentally in 3 dogs with paragonimiasis caused degeneration of *P. westermani* ova and death of adult worms located in pulmonary lesions. Chyu[15] stated that the beneficial effect of using emetine combined with sulfadiazine and other drugs is temporary and should not be considered curative. The cysts of cerebral paragonimiasis should be excised surgically.

SUMMARY

Eight cases of paragonimiasis in children are reported, all of which were caused by ingesting raw crayfish for the treatment of measles. Such a custom, which is prevalent throughout Korea in both city and rural areas, originated with herb doctors. The common practice is to mash and strain the raw crayfish and administer the juice.

1. Cough and wheezing were the first signs of the disease and the children had an x-ray picture of blotchy or fluffy infiltration of the lungs.

2. Six of the 8 patients had x-ray evidence of pleural effusion; one of them had massive empyema. Differential counts of pleural, pericardial, and peritoneal effusions showed 85 to 90 per cent eosinophils.

3. Peripheral blood counts showed moderate to market leukocytosis and an eosinophilia ranging from 11 to 52 per cent, with a mean of 35 per cent.

4. Mild to marked increase in the globulin fraction of the serum protein is almost a constant finding. The total protein may be normal or increased. The albumin and globulin ratio is usually reversed because of an increase in globulin, particularly in the gamma globulin level, and not to a decrease in albumin.

5. Three of the 8 patients had mild to moderate ascites with hepatomegaly which subsided spontaneously within 1 year. Liver function usually was not impaired.

6. Aspiration of the bone marrow in 2 severely ill children showed eosinophilic hyperplasia, in which 70 per cent were mature eosinophils.

7. Subcutaneous biopsy in one revealed an eosinophilic granuloma.

8. Skin tests for *Paragonimus westermani* were positive in all 8. *Paragonimus westermani* ova were demonstrated in 4 of the 8, 3 of them from sputum and 1 from the pus in a brain cyst.

9. The clinical course is a chronic but benign one, and the prognosis is good except in cerebral paragonimiasis which may leave mental retardation, blindness, and motor disturbances.

10. Paragonimiasis is one of the important public health problems in Korea and can be resolved only by extensive public health education. A similarity between the symptoms of visceral larva migrans due to the larvae of *Ascaris lumbricoides* and those due to the larvae of Toxocara is noticed.

In the last month, we have had 3 more patients, all girls, with similar cases. The youngest one was 2 years and 10 months old. One of them belongs in Group 1 and two in Group 3.

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A study of erythropoietin in two types of hemolytic anemia—erythroblastosis fetalis and sickle cell anemia

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THE CONCEPT of a humoral substance active in the regulation of erythropoiesis has now been fairly well established. Initially, Erslev[1] produced a reticulocytosis by injecting plasma from anemic rabbits into normal rabbits. Subsequently, Borsook and associates[2] demonstrated that the active principle was present in boiled plasma extracts. In the course of doing this work, he also showed that it is possible to give the plasma extracts from anemic animals of one species to another species and produce a reticulocytosis and polycythemia. In animals, anemia has been produced by repeated phlebotomy and by injections of phenylhydrazine. The hemolytic anemia induced with phenylhydrazine is the most potent source of erythropoietin,[3] as this plasma factor has been named.

The plasma from patients with various types of blood dyscrasias has been assayed in animals for the presence or absence of erythropoietin. It has been found to be present in the plasma of patients with primary[4, 5] and secondary polycythemia,[5] Cooley's anemia,[6] hypoplastic anemia,[7] immediately following acute blood loss,[7] and in some cases of leukemia.[7] It has also been demonstrated in some, but not all, of the tested cases of sickle cell anemia.[6-8] No erythropoietin has been demonstrated in the plasma of patients with chronic blood loss,[9] chronic renal disease,[7, 10] or in plasma from hematologically normal individuals.

After consideration of the data from animals with hemolytic anemia, and in view of the limited amount of work which has been done with human hemolytic states, we selected for study 2 types of hemolytic processes. Patients with acute acquired hemolytic anemias and those with chronic congenital

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hemolytic anemias constituted the 2 groups studied. Perhaps the most severe acquired hemolytic anemia occurring in children is that found in erythroblastosis fetalis due to an Rh incompatibility between mother and child. Sickle cell anemia was selected as an example of a chronic congenital hemolytic anemia and plasma from patients with this disease was studied. Data on these two types of hemolytic processes, as concerns erythropoietin, is scanty in the literature. Seip,[11] using hematologically normal infants as his recipients, administered very small quantities of plasma obtained from the umbilical cords of normal newborn infants and from erythroblastotic infants. The plasma obtained from both of these donor sources produced a slight reticulocyte rise in the recipient normal infants. A similar rise could not be demonstrated when normal adult plasma was used. As concerns sickle cell anemia, Piliero and co-workers[6] demonstrated erythropoietin activity in the plasma of 1 of the 2 patients tested with sickle cell anemia, but Gurney and his colleagues[7] failed to demonstrate this activity in 1 additional patient. Stohlman[8] was able to demonstrate it in 2 additional patients.

METHODS

Serum was obtained from infants with erythroblastosis fetalis due to Rh or ABO incompatibility at the time of exchange transfusion. All of the blood from an umbilical cord exchange was used and there was no selection of cases on the basis of severity except that the infants had the generally accepted indications for exchange transfusion.[12] The serum was kept in the frozen state until it was processed.

Blood was collected from patients with sickle cell anemia in A.C.D. solution. The plasma was separated and frozen until processed. No attempt was made to obtain blood during a sickle cell crisis. The blood was collected from 4 different patients. Most of the samples were obtained from 1 patient at intervals of 6 weeks to 4 months.

Two different methods were employed to prepare the plasma extract. Initially, a modification of Borsook's method[2] was carried out. Plasma was acidified to pH 5.5 with HCl, boiled for 15 minutes, and filtered. Distilled water in a volume equal to that of the plasma was added to the coagulum, boiled 5 minutes, and filtered. This filtrate was added to the original filtrate. Three such washings were carried out and the combined filtrates were then concentrated by boiling in an open container.

In later experiments, the plasma extract was prepared according to a modification of Gurney's method,[7] utilizing perchloric acid to precipitate the proteins. After cooling the plasma in an ice bath, an equal volume of 10 per cent perchloric acid was added slowly with stirring. The mixture was centrifuged and the precipitate washed three times with one-half volume of 5 per cent perchloric acid. All the supernatants were pooled and dialyzed against running tap water overnight with a final dialysis against distilled water. It was concentrated in a lyophilizer. All plasma extracts were kept in a frozen state until used.

Male Sprague-Dawley rats, weighing 200 to 400 grams, were used as the assay animals. Red cell counts and values for hemoglobin and microhematocrit were determined by conventional methods. The reticulocyte counts were performed by a modified Dameshek technique. All red blood cell counts and reticulocyte counts were done in duplicate. Base line values were obtained at weekly intervals for 3 weeks prior to injections and only animals with stable base line counts were used. Subcutaneous injections of the plasma extract, in a dosage equivalent to 2 ml. of plasma per 100 grams of body weight, were given daily for 4 weeks. Reticulocyte counts were done on the fifth day, and hemoglobin levels, red cell counts, hematocrit determinations, and reticulocyte counts at weekly intervals for 5 to 6 weeks.

Control data were obtained utilizing extracts of normal plasma and saline.

Data were also obtained with extracts of plasma from anemic rabbits. The rabbits were injected with 1 ml. of 2.5 per cent phenylhydrazine solution daily until the

Table I. Reticulocyte response of normal rats to plasma extracts

Type of extract injections	*Number of rats*	*Reticulocytes % (mean ± S.E.)*					
		Time in weeks					
		0	*1*	*2*	*3*	*4*	*5*
Saline	6	4.6 ± 1.4	5.3 ± 2.3	4.2 ± 1.3	4.6 ± 2.2	5.7 ± 3.1	5.1 ± 2.7
Normal	7	4.3 ± 1.0	4.7 ± 0.9	5.0 ± 1.2	6.2 ± 1.4	5.6 ± 2.5	3.3 ± 1.7
EBF*	34	3.7 ± .83	9.3 ± 2.3	6.4 ± 2.5	6.1 ± 3.1	4.5 ± 1.6	3.5 ± 1.4
EBF*	21	3.4 ± .67	4.7 ± 1.0	5.6 ± 2.3	5.2 ± 2.5	4.7 ± 1.9	2.8 ± .97
Anemic rabbit	8	3.6 ± .74	11.4 ± 4.8	5.6 ± 2.4	4.6 ± 1.8	3.9 ± 1.3	4.7 ± 1.2

*Plasma from erythroblastotic infants.

hemoglobin was 4 to 6 Gm. per 100 ml. and the reticulocytes were in the range of 60 to 80 per cent.

RESULTS

1. **Assay of erythropoietin activity in erythroblastosis fetalis.** Erythropoietin can be demonstrated in the plasma of some infants with erythroblastosis fetalis due to Rh or ABO incompatibility as measured by the reticulocyte response in normal rats subsequent to injections with low protein plasma extracts. The plasma from 46 such infants was assayed in 55 normal rats. Table I gives the weekly reticulocyte counts obtained in these assays. The data have been divided into two groups on the basis of the reticulocyte response. One group, consisting of 21 rats (19 different extracts), showed an insignificant reticulocytosis as compared to the response to similar extracts of normal plasma or saline. In the other group of 34 rats (27 plasma extracts), there was a mean reticulocyte increase of 5.6 per cent within 5 to 7 days after the initial injection. By comparison, an average increase of 7.8 per cent was obtained using rabbit plasma extracts from rabbits rendered anemic with phenylhydrazine. The mean reticulocyte increments in the control animals injected with saline and extracts of normal plasma were 0.7 and 0.4 per cent, respectively.

Table II summarizes the changes in red blood counts, hemoglobin values, and hematocrits expressed as the mean increment above the pre-injection values. The increases are comparable to those obtained with plasma from anemic rabbits. As could be expected, no significant change occurred in the group of rats in which erythroblastotic extracts failed to produce a reticulocytosis.

2. **Assay of erythropoietin activity in sickle cell anemia.** As has been found by others, erythropoietin activity was found in some plasma from patients with sickle cell anemia and not in others. Table III lists the results obtained in 16 assays. As can be seen, in 12 instances a reticulocytosis with a mean rise of 4.4 per cent and a concomitant increase in red cell count, hemoglobin, and hematocrit occurred. In the remaining 4 assays, there was no demonstrable erythropoietic activity. Two of the plasma extracts which contained erythropoietin were obtained from 1 patient and the remaining 10 came from another patient at varying intervals of time. Three of the plasma samples with no demonstrable erythropoietin also were drawn from this same patient. The other one which gave negative results was from a fourth patient.

The plasma proteins were removed in the preparation of the extract by 2 different methods—boiling and perchloric acid precipitation. Table IV lists data obtained with these 2 different procedures. The plasmas were from the same erythroblastotic infants previously discussed but in this table they are evaluated in a different manner. There is no significant difference in the response to the 2 methods of preparation.

DISCUSSION

Data have been presented demonstrating erythropoietin in 59 per cent of the plasma samples obtained from infants with erythro-

blastosis fetalis. The remaining 41 per cent showed no erythropoietic activity. Some technical factors may enter into an explanation of this discrepancy. The plasma obtained from the exchange transfusions was of necessity diluted with an unknown quantity of normal plasma. This error is inherent in the technique of doing exchange transfusions. Furthermore, the assay method employed is probably not a sensitive measurement of erythropoietin and it certainly is not quantitative.

Another explanation may rest upon an analysis of the clinical and hematologic status of the infants from whom plasma was obtained. As was mentioned previously, no attempt was made to select only those infants with severe anemia. Of the plasma which gave positive results for erythropoietin, 33 per cent was obtained from infants who showed evidence of an active hemolytic process as depicted by a marked reticulocytosis and increased numbers of nucleated red blood cells in the peripheral blood. In the plasma which gave negative erythropoietin results, 22 per cent was from infants who showed similar evidence of active hemolysis. In the remainder of the cases, the indication for exchange transfusion was hyperbilirubinemia. Therefore, on clinical grounds, it seemed unlikely that erythropoietin would be found in all of the plasma extracts tested.

Jacobson and his associates[13] have postulated that the plasma level of erythropoietin is merely a reflection of an excessive production over the amount utilized by the bone marrow. If this is true, then the plasma level is dependent on the anoxic stimulus to the production of erythropoietin, the body's ability to respond to this stimulus, and the bone marrow utilization of erythropoietin. The kidney also excretes erythropoietin[14-16] and we have no knowledge of the renal threshold for this substance.

It can then be postulated: (1) that in those infants with a severe hemolytic process whose plasma showed no increase in erythropoietin the erythropoietin was being utilized by the bone marrow as fast as it was being produced and (2) that in those with elevated levels, erythropoietin was being released into the plasma faster than it could be utilized by the marrow. In the latter situation, either the hypoxic stimulus was greater, the response to the stimulus was better, or the bone marrow was incapable of greater activity.

Table II. Increments above baseline values of HGB, HCT, and RBC in normal rats following injections with plasma extracts

	Mean increments above base line		
Extract injections	*HGB (Gm./100 ml.)*	*HCT %*	*RBC × 10⁶*
Saline (6)*	0.1	0.3	0.14
Normal plasma (7)	0.1	0.4	0.10
EBF† serum (21)	0.3	0.8	0.26
EBF† serum (34)	1.3	2.8	0.65
Anemic rabbit serum (8)	1.6	2.6	1.04

*Number of rats.

†Plasma from erythroblastotic infants.

Another factor may also play a role here. Mirand[17] and Jacobsen[3] and their colleagues have reported data which indicate that erythropoietin may be inactivated in the liver. Infants who die with severe erythroblastosis frequently have pathologic evidence of liver damage[18, 19] and, in rare instances, have cirrhosis.[20, 21] It is conceivable that some of the more severely involved infants had sufficient liver damage to decrease or prevent the inactivation of erythropoietin, thereby increasing the plasma level.

In the infants with hyperbilirubinemia and slight reticulocytosis as the only evidence of hemolysis, failure of the liver to inactivate erythropoietin may again explain the elevated levels. These infants develop hyperbilirubinemia probably because of the failure of the liver to convert bilirubin to the soluble bilirubin glucuronide, due to a transient decrease in the activity of the enzyme glucuronyl transferase.[22] Other examples of the immaturity of the liver in the newborn could also be cited. Because of this relative immaturity, the infant may not be able to inactivate erythropoietin as effec-

Table III. Response to sickle cell plasma

Plasma extract injections	*Reticulocytes % (mean ± S.E.)* *Time in weeks* 0	1	2	3	4	*Values above base line* *HGB Gm./100 ml.*	*HCT %*	*RBC × 10^6*
Sickle cell (12)*	3.6 ± .36	8.0 ± 2.5	5.4 ± 1.7	5.9 ± 1.9	5.4 ± 2.1	1.1	3.8	0.66
Sickle cell (4)*	3.6 ± 1.0	4.9 ± .77	5.6 ± 1.1	8.4 ± 1.1	3.4 ± .67	0.3	0.5	0.24

*Number of plasma samples assayed.

Table IV. Comparison of response to plasmas from which protein was removed by boiling and by precipitation with perchloric acid

EBF plasma extract*	*Mean values above base line values* *Reticulocytes %—time in weeks* 1	2	3	4	5	*HGB Gm./100 ml.*	*HCT %*	*RBC × 10^6*
Perchloric acid (12)	6.4	3.9	5.0	1.8	1.3	1.4	2.6	0.57
Boiled (16)	7.1	2.2	1.1	0.5	0.1	1.4	3.0	0.67
Perchloric acid (12)	1.2	2.2	2.0	1.4	0.1	0.4	1.1	0.35
Boiled (5)	1.0	2.9	1.6	2.1	0.5	0.3	0.4	0.15

*Plasma from erythroblastotic infants.

tively as adults. There is also more of a hemolytic process than is apparent from the peripheral blood picture since there must be hemoglobin degradation to produce this degree of bilirubinemia. Erythropoietin may be produced by these infants in sufficient quantity to enable the bone marrow to compensate for the hemolysis.

The data are also of interest when evaluated from the standpoint of the newborn infant's ability to produce erythropoietin. Jacobson[23] has demonstrated that fetal mice are capable of producing erythropoietin and that this substance is not furnished to the fetus by the mother via the placenta. We have shown that human infants are capable of responding to an anemic anoxic stimulus by the production of erythropoietin. However, newborn infants are normally polycythemic, probably because of a relative intrauterine anoxia, and might all be expected to have elevated levels of erythropoietin. Seip[11] injected into hematologically normal infants small quantities of plasma obtained from the umbilical cords of the normal newborn. A slight reticulocytosis was produced in the recipients. We were not able to confirm this finding in all instances, even when only the blood obtained from infants 4 hours of age or less was considered. In this age group, negative as well as positive results were obtained. More studies need to be done on blood obtained from the umbilical cords of normal newborn infants.

Our findings on the plasma of patients with sickle cell anemia corroborate the work of others.[6-8] We found erythropoietin in 12 of the 16 plasma samples tested, representing positive results in 1 patient, both positive and negative in another, and negative results in a third.

Patients who are homozygous for sickle hemoglobin have a persistent severe anemia with a hemoglobin range of 6 to 9 Gm. per 100 ml. This anemic anoxia should provide an almost continuous stimulus to the production of erythropoietin. Thus, it is not surprising to find erythropoietin in the plasma of some of these patients. The liver factors already discussed may also play a role in sickle cell anemia since hepatic disease is frequently associated.[24]

The instances where no erythropoietin was found might be explained on the basis of an equilibrium between the production and utilization of this substance. The fact

that we obtained both positive and negative results on the same patient at various times suggests that levels may vary from time to time.

It would be of considerable interest to be able to follow a patient from the onset of an aplastic crisis until recovery was complete. Data on patients with hypoplastic and aplastic anemias[7, 10, 15, 25] suggest that high plasma erythropoietin levels are found where there is erythroid bone marrow depression, probably due to a decreased utilization by the marrow. Perhaps, during an aplastic crisis in either sickle cell anemia or hereditary spherocytosis, elevated plasma levels could also be found.

The comparison of the data obtained with the two different methods of preparing the plasma extract is in keeping with data previously reported by others.[26] The substance we were assaying is heat stable, nondialyzable, and it is not precipitated by perchloric acid or boiling. Rambach, Alt, and Cooper[27, 28] have data which suggest that erythropoietin is a mucoprotein or that a mucoprotein acts as a carrier for the active principle. Goldwasser and White[29] suggest that it is an α_2 glycoprotein.

SUMMARY

Plasma erythropoietin has been demonstrated in two types of human hemolytic processes—erythroblastosis fetalis and sickle cell anemia.

It was demonstrated in the plasma of 27 of the 46 infants tested with erythroblastosis fetalis. There was no direct correlation between the severity of the anemia in these infants and the potency of the erythropoietic activity of the plasma.

Erythropoietin was also demonstrated in 12 of the 16 plasma samples from patients with sickle cell anemia.

Possible explanations are discussed for the finding of erythropoietin in the plasma of some patients with hemolytic anemia and not in others.

The authors wish to thank Dr. Hugh Chaplin for supplying them with plasma from his patients with sickle cell anemia.

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A reliable qualitative urine coproporphyrin test for lead intoxication in young children

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WE WISH to report a qualitative technique for urine coproporphyrin estimation which has proved reliable, simple, and sensitive in our hands for screening children in whom lead poisoning is suspected. Derangement of porphyrin metabolism associated with an increased excretion of coproporphyrin III in the urine is an early and constant finding in lead intoxication.[1, 2, 3] Early diagnosis and treatment are essential if fulminant lead encephalopathy with its high mortality and neurological sequelae rates is to be avoided.[4, 5] Procedures for the detection of coproporphyrinuria in the diagnosis of plumbism in children based on the method of de Langen and ten Berg[1] have been unreliable in our hands and in the experience of others.[6] In such procedures coproporphyrin is estimated in ether extracts of urine. The method reported in this paper is based upon the excellent quantitative procedure of Schwartz and associates[7] in which the estimation is made in hydrochloric acid.

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CLINICAL MATERIAL

This report is based upon the study of 258 subjects seen at the Outpatient Department of the Harriet Lane Home between June, 1958, and June, 1959. Their ages ranged from 8 to 63 months. The children came from slum areas of Baltimore where houses are old and lead intoxication is endemic. A history of either wall plaster or paint ingestion or of clinical features suggestive of lead intoxication was present. Among these 258 patients, 44 had acute lead intoxication, 52 had increased absorption of lead but were asymptomatic, and 162 showed no evidence of increased lead absorption according to previously published criteria.[8] Cases with a previous diagnosis of lead poisoning were excluded from this study.

The studies on the relationship between urine coproporphyrin concentration and the results obtained with the qualitative screening test are based upon analyses of 103 urine samples obtained from a previously reported group of normal children and children with lead poisoning.[9]

METHODS

A specimen of urine was collected from each child and tested for coproporphyrin within 15 minutes of voiding. A blood sample was obtained by venipuncture with the use of a lead-free needle and tube. Whole blood lead concentration was determined by the Division of Laboratories of the Baltimore City Health Department by a wet-digestion dithizone technique.[10]

The qualitative urine coproporphyrin screening test which was adapted from the quantitative procedure of Schwartz and associates[7] is as follows:

A. Reagents.

1. 1.5 N hydrochloric acid
2. Ether
3. Glacial acetic acid
4. 0.1 per cent iodine in 95 per cent alcohol w/v

B. Equipment.

1. Wood's lamp
2. Pyrex test tubes (18 by 150 mm.). The test tubes used must be of the same diameter as the tubes in which standard reference solutions are kept. Tubes 18 to 20 mm. in diameter are preferred. Soft glass tubes must not be used.
3. p-Hydrion test paper, Type D (range: pH 3.0 to 5.5).
4. Pipettes, suitable for measuring 5 ml. and 0.25 ml.
5. Droppers with rubber bulbs suitable for aspirating.

C. Procedure.

1. Measure a 5 ml. sample of urine and transfer it to a Pyrex test tube (18 by 150 mm.).

2. Carefully acidify the urine sample to pH 4.0 with glacial acetic acid. Usually 2 to 3 drops of glacial acetic acid are required. Use p-Hydrion test paper as indicator. Occlude the top of the tube firmly with the thumb. Then shake the tube vigorously 10 to 15 times to facilitate complete expulsion of carbon dioxide gas bubbles from the acidified urine. This is essential if emulsions are to be avoided in Step 4.

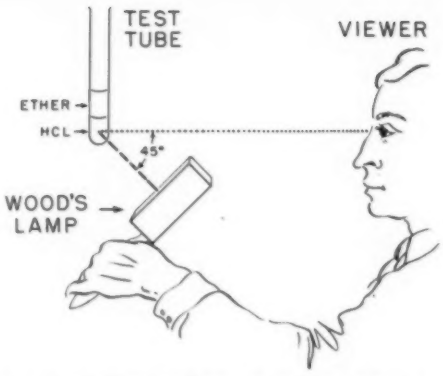

Fig. 1. Optimal positions of viewer, tube, and Wood's lamp for estimating fluorescence.

3. Add 5 ml. of ether down the side of the tube.

4. Again occlude the top of the tube with the thumb. Then shake the tube vigorously 30 times longitudinally pressing with the thumb in order to maintain pressure in the tube.

5. With the thumb still in place hold the tube vertically until the urine and ether layers separate completely. By maintaining the pressure in the tube during Steps 4 and 5, one can minimize ether-urine emulsion. Aspirate the ether layer into a clean tube with a pipette and aspirator bulb. Take especial care not to contaminate this ether fraction with the lower urine layer which may contain pigments that can interfere with subsequent estimation of fluorescence intensity. Should an emulsion form, one can separate the ether layer from the urine readily by centrifugation for a few minutes. Alternatively, one may start again with a fresh aliquot of urine and use a greater volume of ether for the initial extraction.

6. Add 5 ml. of 1.5 N hydrochloric acid to the ether fraction. Carry out the extraction as before, again ensuring that the pressure in the tube is maintained by occluding the top with the thumb during shaking and separation.

7. Examine the tube under a Wood's lamp in a darkened room, taking care to direct the

rays of the lamp away from the viewer's eyes while holding the tube close to the lamp. Estimate the intensity of fluorescence in the hydrochloric acid (lower) layer by comparison with standards of known coproporphyrin concentration.* Standard and sample tubes must be of the same diameter for reliable comparison. Fluorescence is best observed at an angle of 45° to the incident ultraviolet light as shown in Fig. 1. The result is expressed according to the arbitrary scale shown in Table I.

8. In some urine samples a significant portion of the total coproporphyrin may be present in a nonfluorescent state, so that maximal fluorescence is not detected at Step 7. Treatment with the proper quantity of iodine converts these precursors to fluorescent coproporphyrin. After estimating the fluorescence in Step 7, add exactly 0.25 ml. of 0.1 per cent iodine in 95 per cent alcohol weight by volume to the ether-hydrochloric acid mixture. Use of an excessive amount can result in some destruction of coproporphyrin. Then shake the tube with the same precautions as in Step 4. After separation is complete, re-examine the hydrochloric acid layer under the Wood's lamp. An increase in fluorescence intensity may be observed. If diminution in fluorescence intensity occurs, it should be considered the result of technical error and disregarded. Take the maximal fluorescence observed as the final result (Step 7 or 8).

*Throughout this study fluorescence intensity was estimated by visual comparison of the sample with reference solutions in sealed tubes containing 0.1γ, 0.2γ, and 0.5γ of coproporphyrin per milliliter in 1.5 N HCl. Mesoporphyrin IX is more readily available commercially than coproporphyrin and is suitable for use as a reference standard in this test. The authors have been informed that L. Light and Co., Poyle Colnbrook, Slough, Bucks, England, can supply prepared mesoporphyrin IX reference solutions in sealed Pyrex tubes for this test. Directions for the use and preparation of coproporphyrin and mesoporphyrin IX standards are given in Appendix I.

If neither mesoporphyrin IX nor coproporphyrin III reference solutions are available, the following may serve as a guide. One-tenth γ per milliliter is the lower limit of coproporphyrin concentration at which a faint reddish fluorescence in the blue solution can be detected by the average viewer. Solutions containing more than 0.5γ per milliliter appear entirely orange-red. By appropriate dilution of the hydrochloric acid extract of the sample, these two concentrations can be approximated.

The technique of this test is simple and easily acquired. The instructions, however, must be followed carefully or false results may be obtained. The reagents and apparatus used in this test are available readily and the whole procedure takes only a few minutes.

RESULTS

In order to determine the accuracy of this technique, coproporphyrin concentration was determined in 103 urine samples both by this qualitative technique and by the quantitative procedure of Schwartz and co-workers.[7] The data in Fig. 2 show that the qualitative estimates approximate the quantitative values. Normally, the concentration of

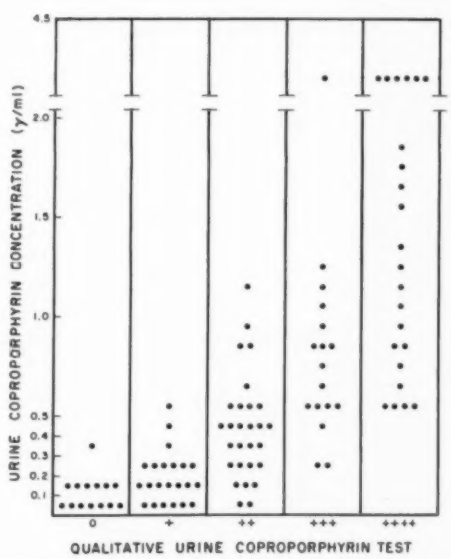

Fig. 2. Correlation between urine coproporphyrin concentration and qualitative screening test.

For each of 103 urine samples the result of the qualitative test was plotted against the urine coproporphyrin concentration as determined quantitatively. It is apparent that the qualitative technique is sensitive to clinically significant differences in coproporphyrin concentration. Thirty-four of 37 samples estimated as +++ or ++++ contained coproporphyrin in excess of 0.5 γ per milliliter. Conversely, only 1 of 36 samples read as 0 or + contained coproporphyrin in excess of 0.5 γ per milliliter. 0 or + readings were found in normal individuals. The ++ readings showed considerable variation.

Table I. Arbitrary scale of fluorescence intensity of coproporphyrin solutions

Arbitrary scale	*Color*	*Approximate quantitative equivalent of coproporphyrin*
0	Blue-violet	Less than 0.1 γ/ml. of urine
+	Faint blue-orange	0.1 γ/ml. of urine
++	Blue-orange	0.2 γ/ml. of urine
+++	Orange-red	0.5 γ/ml. of urine
++++	Deep orange-red	More than 0.5 γ/ml. of urine

Table II. Comparison of reliability of coproporphyrin estimation in ether and hydrochloric acid extracts*

	UCP (γ/ml.)†	*No. of samples*	*Qualitative estimation (arbitrary units)*				
			0	+	++	+++	++++
Ether extracts	< 0.5 γ/ml.	57	45	11	1	0	0
	> 0.5 γ/ml.	46	7	7	12	7	13
Hydrochloric acid extracts	< 0.5 γ/ml.	57	14	21	19	3	0
	> 0.5 γ/ml.	46	0	1	9	14	22

*These data are based upon paired estimates of fluorescence intensity in 103 urine samples from normal children and from children with lead poisoning. In each group the samples have been divided according to their coproporphyrin concentration as measured quantitatively by the technique of Schwartz and associates.[7] Note the inaccuracy of coproporphyrin estimation in the ether extracts in samples containing greater than 0.5 γ per milliliter. Note that both false-positive and false-negative results are minimized in the hydrochloric acid extracts.

†UCP = Urine coproporphyrin concentration.

Table III. Comparison of intensity of coproporphyrin fluorescence in hydrochloric acid and ether extracts as related to whole blood lead concentration*

Whole blood lead concentration (mg./100 Gm.)		*Qualitative urine coproporphyrin test*					*No. of cases*
		0	+	++	+++	++++	
0.10 and greater	Hydrochloric acid	0	0	0	13	16	29
	Ether	19	0	0	1	9	
0.06 to 0.099	Hydrochloric acid	14	13	16	18	6	67
	Ether	64	0	0	2	1	
0.059 and less	Hydrochloric acid	92	51	18	1	0	162
	Ether	162	0	0	0	0	

*In all cases duplicate estimates of the coproporphyrin fluorescence intensity were obtained. In one sample the reading was made in the ether extract while in the other fluorescence was estimated in the hydrochloric acid extract.

It is apparent that the complete procedure (estimation of fluorescence in the hydrochloric acid extract) is far more reliable for detecting patients with elevation of whole blood lead concentration.

coproporphyrin in urine does not exceed 0.2 γ per milliliter and concentrations in excess of 0.5 γ per milliliter are definitely abnormal. It can be seen in Fig. 2 that concentrations in excess of 0.5 γ per milliliter can be readily distinguished from those of less than 0.2 γ per milliliter by the qualitative technique.

The technique was then evaluated in the Outpatient Department as a screening test on 258 children in whom the diagnosis of lead poisoning was considered. A correlation was found between a moderate to a marked elevation of whole blood lead concentration and a urine coproporphyrin test result of +++

and ++++. The results for the entire group are shown in Fig. 3 where the whole blood lead concentration is plotted on a logarithmic scale on the ordinate against the result of the urine coproporphyrin test on the abscissa.

In 68 of 69 cases of acute lead encephalopathy previously reported[4] the whole blood lead concentration was 0.10 mg. per 100 Gm. or greater. In the present study 29 subjects had whole blood lead concentrations of 0.10 mg. per 100 Gm. or over; in all of these the qualitative urine coproporphyrin test gave a +++ or ++++ result (Fig. 3). Of the 162 subjects with no significant elevation of whole blood lead concentration (i.e., not exceeding 0.06 mg. per 100 Gm.), all but 19 had a normal (0 or +) qualitative urine coproporphyrin test and only 1 had a +++ or ++++ result. Of the 67 subjects with intermediate elevations of whole blood lead concentration (0.06 to 0.099 mg. per 100 Gm.), 24 gave a +++ or ++++ result and 16 a ++ result.

In order to determine the necessity for the hydrochloric acid extraction (Steps 6 to 9) in this qualitative technique, all urine specimens were analyzed in duplicate. In one aliquot, fluorescence intensity was estimated in the ether extract at the end of Step 5. In the other aliquot the entire procedure was carried out and fluorescence intensity was estimated in the hydrochloric acid extract. The results of this part of the study are shown in Tables II and III. The data in Table II show that coproporphyrin concentration cannot be estimated accurately by fluorescence intensity in ether extracts of urine. Among 46 samples in which the quantitatively determined coproporphyrin concentration exceeded 0.5 γ per milliliter, 36 gave a +++ or ++++ reading in hydrochloric acid, whereas only 20 of them gave a +++ or ++++ reading in ether. More important is the observation that 14 of these 46 abnormal samples gave a normal result (0 or +) in ether. When the procedure was carried through to completion and fluorescence intensity was estimated in the hydrochloric acid extracts, only 1 of these 46 abnormal

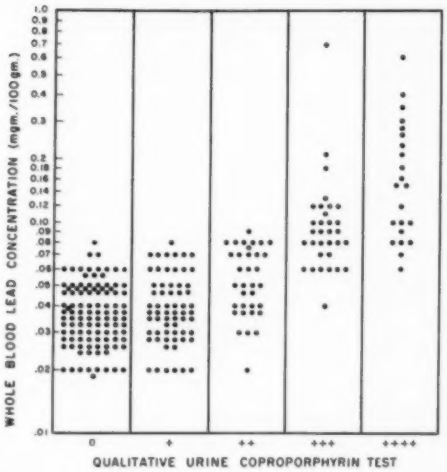

Fig. 3. Relation between whole blood lead concentration and results of the qualitative urine coproporphyrin test.

For each of the 258 patients examined, the results of the qualitative urine coproporphyrin test on the abscissa were plotted against the whole blood lead concentration on a logarithmic scale on the ordinate. All patients with potentially dangerous elevation of the whole blood lead concentration (0.10 mg. per 100 Gm. or over) gave a +++ or ++++ result. Where the whole blood lead concentration fell within the normal range (less than 0.06 mg. per 100 Gm.), the vast majority gave normal (0 or +) results.

samples gave a + reaction and none gave 0.

The data in Table III demonstrate the practical implications of this finding. Of the 29 subjects with whole blood lead concentration of 0.10 mg. per 100 Gm. or greater, 19 gave a 0 result at the stage of the ether extraction, while all gave +++ or ++++ results when fluorescence intensity was estimated in the hydrochloric acid extract. In the entire group, 96 subjects had whole blood lead concentrations of 0.06 mg. per 100 Gm. or more. Of these only 13 gave a +++ or ++++ result at the ether stage while 53 gave a +++ or ++++ result with the complete procedure. It is apparent that the hydrochloric acid extraction step in this procedure is essential.

DISCUSSION

This screening technique for the estimation of coproporphyrin concentration in

urine is simple. There are, however, certain critical steps in the analysis which must be performed carefully. An appreciation of some of the basic physicochemical properties of the porphyrins will clarify the need for the various steps in the procedure. Porphyrins are amphoteric compounds whose isoelectric points lie in the range pH 3.0 to 4.5.[11] At its isoelectric point coproporphyrin is extracted readily from aqueous solutions (urine) into ether. The pH must, therefore, be controlled carefully in this initial extraction. Porphyrins are extracted from ether by mineral acids and by neutral aqueous solvents. Coproporphyrin is excreted in the urine in several forms, including nonfluorescent coproporphyrinogens and a zinc-porphyrin complex,[11] the proportions of which may vary from sample to sample.[7] All may readily be converted to fluorescent coproporphyrin. Oxidation with iodine quantitatively converts coproporphyrinogen to coproporphyrin. The zinc-coproporphyrin complex is split more readily and extracted from ether with 1.5 N hydrochloric acid than with lower concentrations of acid.[7] The intensity of the fluorescence of porphyrins in aqueous solution varies with the pH. Maxima of fluorescence are observed in the range pH 1.0 to 2.0; minima of fluorescence are observed in the range pH 3.0 to 4.5.[11, 12] Coproporphyrin is stable in neutral or slightly alkaline urine, but losses occur if it is kept in acid urine for any period of time.[7] For this reason the urine should be either neutralized or examined as soon as voided and the ether extraction at pH 4.0 carried out as rapidly as possible after acidification of the urine with acetic acid.

Of the greatest practical importance is the fact that interfering substances which fluoresce green are extracted readily from acid urine into ether. To ensure that these substances are not extracted from ether into hydrochloric acid, a sufficient concentration of acid must be used.[7] Although 0.1 N hydrochloric acid is universally available in clinics, we have used 1.5 N hydrochloric acid as in the quantitative procedure of Schwartz and co-workers.[7]

In techniques based upon the method of de Langen and ten Berg,[1] fluorescence intensity is measured in the initial ether extract. Although several investigators[1, 2, 3] have found this method satisfactory for the screening of industrial workers exposed to lead, Bradley and associates[6] found it unreliable for detecting children with abnormal amounts of lead in the blood. This is not surprising in view of the analytical considerations just outlined. De Langen and ten Berg[1] suggested several methods for removing the noncoproporphyrin fluorescent substances from the ether extract, but these are too cumbersome for practical purposes. In the present study, removal of interfering fluorescent substances is achieved simply by extracting the coproporphyrin from ether into hydrochloric acid. Using a similar technique in the study of industrial workers, Shiels and co-workers[13] have reported significant correlation between the semiquantitative estimation of urine coproporphyrin and urine lead concentration, blood lead content, and, to a lesser degree, stippled cell counts.

The data shown in Tables II and III demonstrate the unreliability of estimating coproporphyrin by fluorescence intensity in ether extracts of urine. The greater sensitivity in hydrochloric acid extracts is readily apparent.

All qualitative tests have their limitations and must be interpreted with care. In lead poisoning it is the total daily urine coproporphyrin output[9] rather than its concentration in casual urine samples which is the significant measurement. Various authors[14, 15, 16] have reported that urine coproporphyrin excretion is about 1 γ per 24 hours per pound of body weight in healthy children. This output is consistent with concentrations ranging between 0.1 and 0.2 γ per milliliter of urine which, in turn, are equivalent to + and ++ readings in the technique presented. Concentrations in excess of 0.5 γ per milliliter are indicative of excessive coproporphyrin excretion. Such concentrations give readings of +++ and ++++ with this technique. Readings of ++ must be interpreted with caution; they may represent a normal or moderately

increased urine coproporphyrin excretion (Fig. 2) as may be found in other diseases. Review of Fig. 3 shows that ++ readings were found in a number of subjects with intermediate elevations of whole blood lead concentrations (0.06 to 0.099 mg. per 100 Gm.). If plumbism is suspected strongly such readings call for further investigation.

The chief value of the qualitative urine coproporphyrin test is its ability to detect those patients with dangerous amounts of lead in the tissues in whom encephalopathy may be imminent though the clinical diagnosis is obscure. In our experience this test was uniformly positive in such patients, whereas other quickly available ancillary investigations were not.

Parents of the 258 children whose urine was examined for coproporphyrin were questioned specifically for a history of ingestion of paint flakes or crumbling plaster. Pica was denied in 15 of the 29 children with a whole blood lead concentration of 0.10 mg. per 100 Gm. and over. Abdominal x-rays were obtained for 20 children with whole blood levels of 0.10 mg. per 100 Gm. and over; in 6 of these there was no evidence of intra-abdominal opaque material compatible with lead-containing fragments. In 18 children for whom x-rays of the long bones were available, 7 showed no evidence of increased density of the metaphysis. A review of 89 cases of acute lead encephalopathy reported earlier[8] provided further evidence of the unreliability of these ancillary investigations for the early diagnosis of acute lead intoxication: thus, pica was denied in 14 of 48 cases; x-rays of the abdomen showed no evidence of radiopaque fragments in 8 of 32 cases so examined, and x-rays of the long bones showed no increase in the metaphysial density in 12 of 53 cases.

Increased excretion of coproporphyrin in the urine is found uniformly in lead poisoning; this also occurs in many other diseases. Infections, trauma, rheumatic fever, and various hematologic disorders may evoke a two- to threefold increase in the total daily excretion of coproporphyrin in the urine.[14] The sensitivity of the qualitative test outlined is such that a 0, +, or ++ result is obtained in most of them. Only if the urine is quite concentrated will coproporphyrin concentrations of 0.5 γ per milliliter (+++ or ++++ readings) be encountered. The value of the test in screening patients for acute plumbism lies in the fact that lead intoxication can produce a much greater increase in the daily urine coproporphyrin output than do the diseases just cited. In potentially serious cases of plumbism the amounts excreted are usually 5 times and frequently more than 10 times the normal output.[9] In these patients coproporphyrin concentrations in excess of 0.5 γ per milliliter are found regularly even in dilute casual urine samples. Only in patients with severe hepatocellular damage (acute infectious hepatitis and liver damage caused by poisons such as carbon tetrachloride), inborn errors of porphyrin metabolism, and possibly bulbar poliomyelitis are amounts of coproporphyrin excreted in the urine which are comparable to or greater than the amounts found in lead poisoning. Positive (+++ or ++++) results with the present technique are to be expected in these diseases. When clinical diagnosis is obscure, all must be considered and the pertinent diagnostic procedures carried out. Similarly, it must be stressed that this test should not replace blood lead determinations or other ancillary investigations which are necessary for a more precise and comprehensive evaluation of each patient. Because this test is simple, rapid, and regularly positive in acute lead poisoning and the result immediately available, it is useful especially in those cases where the clinical diagnosis is uncertain and where immediate treatment may be indicated.

CONCLUSIONS

1. A technique is described for the detection of increased amounts of coproporphyrin in urine. It is easy to perform and has proved most useful in the early diagnosis of lead poisoning.

2. Some principles of porphyrin analysis are discussed. Evidence is presented to show that estimation of coproporphyrin in initial

Table IV. Spectral absorption of mesoporphyrin IX at its maximum (400 to 402 mμ) in the Soret band in 1.5 N HCl

Concentration of mesoporphyrin IX	*Beckman DU (0.18 mm. slit) O.D.*	*Beckman DK (0.08 mm. slit) O.D.*
0.14 γ/ml.	0.10	0.11
0.28 γ/ml.	0.20	0.22
0.70 γ/ml.	0.50	0.55

Table V. Solutions of approximately equivalent fluorescence intensity in 1.5 N HCl

Coproporphyrin III	*Mesoporphyrin IX*
0.1 γ/ml.	0.14 γ/ml.
0.2 γ/ml.	0.28 γ/ml.
0.5 γ/ml.	0.70 γ/ml.

ether extracts of urine is not reliable. In the technique presented, coproporphyrin is extracted from the ether into hydrochloric acid for the estimation of fluorescence intensity. Under these conditions far greater discrimination between samples of high and low coproporphyrin concentration can be achieved.

3. With this technique a positive coproporphyrin result (+++ or ++++) was present uniformly in patients with whole blood lead concentration greater than 0.10 mg. per 100 Gm., whereas in a number of these patients abdominal and long bone x-rays were negative for evidence of plumbism and the history of pica was denied.

APPENDIX I

Use and preparation of coproporphyrin and mesoporphyrin reference solutions. Reference solutions should be kept in sealed Pyrex tubes of the same diameter as those in which samples are analyzed. These solutions should be kept cool and in the dark when not in use. They may be checked for stability periodically on the basis of the spectral absorption data given below, if a suitable fluorimeter is not available.

Commercial samples of porphyrins are often of uncertain purity. They are apt especially to be contaminated by inorganic salts, so that some criterion other than weight is necessary for assay of a commercial sample's porphyrin content. To prepare reference solutions for this test, dissolve approximately 2 mg. of porphyrin in 2 L. of 1.5 N HCl. Allow 1 week to effect solution. Filter off any insoluble material with the use of a fritted glass filter. Determine the actual porphyrin content on the basis of the special absorption data for pure coproporphyrin and mesoporphyrin given below.

Jope and O'Brien* report that the spectral absorption of coproporphyrins I and III in 1.5 N HCl at 403.5 mμ (maximum) is $E^{1\%}_{1\ cm.} = 7{,}450$ when measured with slit width < 0.1 mm.

Since mesoporphyrin IX is available more readily commercially than coproporphyrin and is suitable as a reference standard in this test, the data in Table IV may aid in the preparation of mesoporphyrin IX reference solutions.

Approximate coproporphyrin-mesoporphyrin IX fluorescence intensity ratios (Table V) were determined in a Calelectron photofluorimeter[7] for the concentrations of coproporphyrin used as reference standards in this test.

Observe that a concentration of mesoporphyrin IX approximately 1.4 times greater than that of coproporphyrin III is required to yield fluorescence of equivalent intensity.

These data are based upon the analysis of a highly purified sample of mesoporphyrin IX dihydrochloride which was donated by Dr. Winslow S. Caughey, Department of Physiological Chemistry, The Johns Hopkins University School of Medicine. From this sample the molar extinction coefficient of mesoporphyrin IX in 1.5 N HCl was calculated as 4.4 times 10^5 at its maximum (401 mμ) in the Soret band.

A sample of mesoporphyrin IX purchased from L. Light and Co., Poyle Colnbrook, Slough, Bucks, England, was prepared as described above. The filtered solution had the same spectral absorption-fluorescence ratio as that of the highly purified sample, so that it was considered satisfactory for this test.

We wish to express our appreciation to Dr. Emmanuel Kaplan of the Baltimore City Health Department in whose laboratory all of the blood lead determinations reported in this study were performed.

We acknowledge with pleasure the kind assistance of Dr. Winslow S. Caughey, Department of Physiological Chemistry, The Johns Hopkins

*Jope, E. M., and O'Brien, J. R. P.: Biochem. J. 39: 239, 1945.

University School of Medicine, in that phase of this study concerned with mesoporphyrin reference solutions.

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Voiding urethrography: an integral part of intravenous urography

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THE DIAGNOSTIC importance of voiding urethrography generally is not appreciated by either the pediatrician or the radiologist. By visualization of radiopaque urine flowing through the urethra from the bladder, the radiologist can evaluate urethral function better than can the cystoscopist. With the arrival of the newer concentrated contrast media for better visualization of the urinary tracts and the use of carbonated beverages to push aside the extraneous bowel shadows that frequently overlie the kidneys,[1] it is possible usually to avoid doing the painful unphysiologic retrograde pyelogram.[2] Also, with these new contrast media it is possible to visualize radiographically urine flowing through the urethra. Accordingly, with a single intravenous injection of a sterile radiopaque dye, followed by the ingestion of a carbonated beverage, and with a film that has been exposed while the patient voids the opaque urine, it is possible to document in a physiologic manner not only the anatomy but also the transport of urine in the urinary system. While this technique may be tedious, the pediatric patient benefits by avoiding anesthesia, pain, and lower urinary tract instrumentation which frequently leads to urinary infections.

With the advent of cineradiography, it is evident that the function of the lower urinary system is very complicated and that much is unknown. In this nebulous area the authors are aware that "today's facts" frequently become false legends tomorrow. Today we accept the postulate that in the absence of infection and neurogenic disorders, a dilatation in the urinary system is the result of a significant obstruction to urine flow. By making the voiding urethrogram routine in our intravenous urogram studies in males, we have found, as have others before us,[3, 4] not only the classical tight posterior urethral valve associated with irreparable kidney damage, but also anterior as well as posterior urethral valves which have caused varying degrees of bladder, ureteral, and renal difficulties. The latter valves are important clinically because incision or excision of the valves allows the urinary system in the child to return to normal. The following case reports are some examples of correctable lesions found in this hospital during the last year.

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CASE REPORTS

Case 1. A 4-year-old Negro boy was admitted to The Children's Hospital of Philadelphia with a 9-month history of intermittent episodes of fever to 105° F. One week prior to admission, he again had a high temperature. On this occasion the mother noted that the patient's urine was cloudy and foul smelling and associated with dysuria and frequency (Fig. 1).

On physical examination, the patient appeared acutely ill, with a temperature of 104° F., and generalized erythema. Physical examination was otherwise normal.

Urinalysis revealed myriads of white blood cells and urine culture showed a heavy growth of *Escherichia coli.*

The minimal clubbing in the superior calyx of the left kidney (Fig. 1, *A*) is indicative of pyelonephritis. Extreme dilatation of the entire posterior urethra is shown in the voiding urethrogram (Fig. 1, *B*). Although the actual valve is not seen, this dilatation is typical of a posterior urethral valve extending from the verumontanum to the external sphincter and gives rise to partial obstruction.

Case 2. A 4-year-old white boy of normal growth and development was examined by intravenous urography solely because of inability to urinate with a forceful stream.

Fig. 2, *A* is the 15-minute film following the intravenous injection of 15 ml. of 50 per cent Hypaque. The kidneys are grossly normal, and the ureters are not dilated. There is minimal blunting of the superior calices on the left side which suggests the possible presence of minimal pyelonephritis. A subsequent urine culture was negative. The postvoiding film showed the bladder to be empty. If a voiding urethrogram had not been obtained, the diagnosis would have been missed.

Fig. 2, *B* is a film obtained during micturition. In the middle of the anterior urethra, the diameter abruptly narrows (arrow). Actually the valve can be seen on this film, but at first its significance was not realized.

From the urologic standpoint, it was necessary to know whether the entire anterior urethra from the zone of transition distally to the meatus was narrow or whether this apparent narrowing was caused by in-

Fig. 1. Case 1, a 4-year-old Negro boy with a 9-month history of intermittent episodes of fever, dysuria, frequency, and foul-smelling urine. *A*, Fifteen-minute film of an intravenous urogram showing minimal clubbing in the superior calyx of the left kidney (arrow), indicative of pyelonephritis. *B*, The voiding urethrogram demonstrating extreme dilatation of the entire posterior urethra to the external sphincter (arrow). The actual valve causing the partial obstruction is not seen.

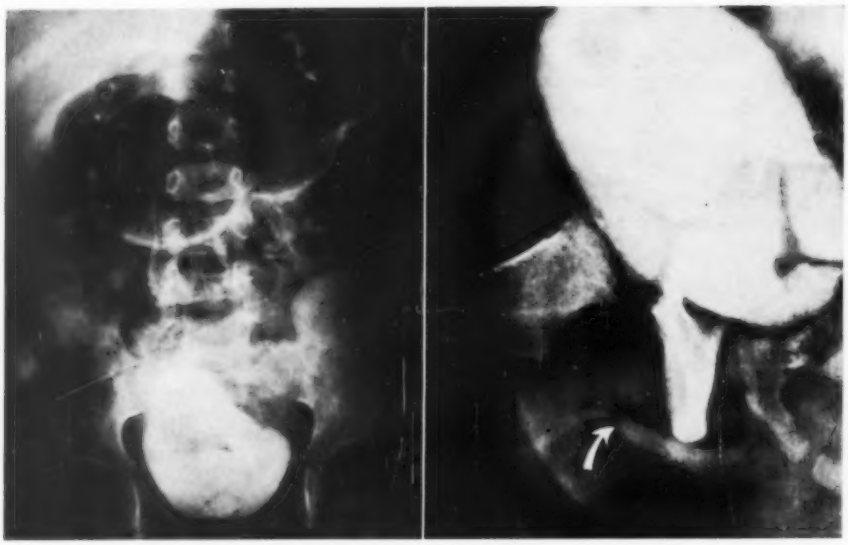


Fig. 2. Case 2, a 4-year-old boy examined because of inability to urinate with a forceful stream. *A*, Fifteen-minute film of an intravenous urogram showing only minimal blunting of the superior calices on the left side, possibly secondary to pyelonephritis. *B*, Voiding urethrogram showing an abrupt narrowing of the stream in the anterior urethra (arrow).

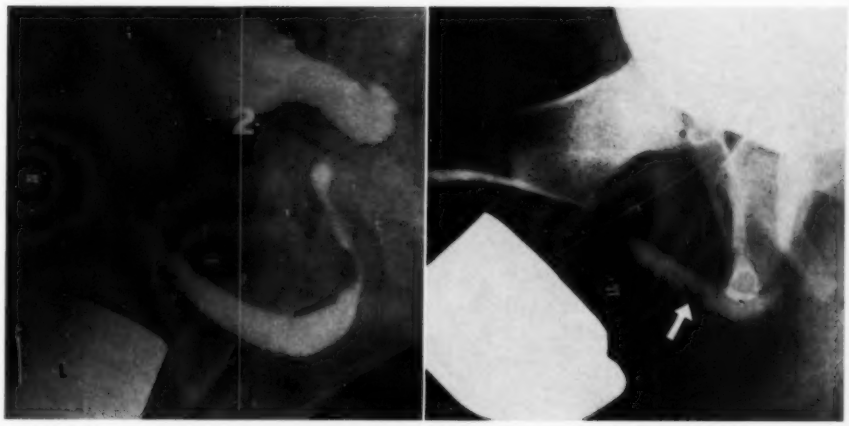
sufficient urine passing the obstruction to distend the rest of the urethra. This is similar to the problem so often encountered in the esophagus where there is an apparent long stricture, but where in reality there is a short stricture and insufficient contrast medium flowing by the obstruction to distend the distal esophagus. A retrograde urethrogram was therefore necessary to complete the study.

Fig. 2, *C* is a film obtained while Iodochlorol was being injected into the urethra by means of a catheter inserted in the tip of the anterior urethra. It is obvious that the entire anterior urethra can dilate and the stricture, or narrowed zone, is not visualized. However, a strange radiolucent curvilinear line is seen on the ventral wall (arrows). The significance of this line was still not realized at this stage of the examination.

The bladder then was filled with a 25 per cent Hypaque solution and again a voiding urethrogram was obtained. In Fig. 2, *D* the film of this second voiding urethrogram, the entire problem is explained. The curvilinear line is again seen (arrows), and at its distal radiolucent end is the obstruction. The curvilinear radiolucent line is the shadow produced by an anterior urethral valve.

Case 3. A 12-year-old white boy entered the hospital with a 2-week history of swelling of the feet, fever up to 101° F., pains in the calves, and periorbital edema. The only complaint relating to the genitourinary system was a 2-day period of difficulty in voiding because of dysuria. At 10 years of age, because of persistent low-grade pyuria, an intravenous urogram was done elsewhere. That study showed some blunting of the calices of the upper pole of the right kidney. We believe this finding was secondary to pyelonephritis, but no therapy was given at the other institution. Because of persistent minimal pyuria, an intravenous urogram was requested on the present admission.

Fig. 3*A* is the 30-minute film following the intravenous injection of 25 ml. of 50 per cent Hypaque. The left kidney is normal, but on the right there is a severe dila-



C *D*

Fig. 2, *C,* Retrograde urethrogram showing no stricture of the anterior urethra. There is a peculiar radiolucent curvilinear line on the ventral wall of the urethra (between the two arrows). The testicles are protected by a lead shield (*L*). *D,* Voiding urethrogram after the bladder was filled by retrograde injection. Again the abrupt narrowing of the anterior urethra is seen at the distal end of the curvilinear line (arrow). The curvilinear line is an anterior urethral valve. Again the testicles are protected with a lead shield.

tation of all the calices. The renal cortex of this kidney still appears normal. The ureters and bladder are normal, and the patient subsequently emptied the bladder completely upon voiding. If a voiding urethrogram had not been obtained, the diagnosis would have been pyelonephritis of the right kidney, cause unknown.

Fig. 3, *B* is a film obtained while the boy was voiding. The posterior urethra is abnormally dilated, and in the middle of the urethra the diameter abruptly narrows (distal arrow). Initially the film suggested a posterior urethral valve with an unusual elongation of the posterior urethra. If this were all posterior urethra, however, it was less dilated than is usually the case with a posterior urethral valve. As an alternative, it seemed probable that the external sphincter was proximal to the narrowed zone (arrow marked *E.S.*). If this were the case, an anterior urethral valve was present, and a retrograde urethrogram was indicated.

Fig. 3, *C* is a film obtained while injecting 15 per cent Hypaque into the urethra by means of a catheter inserted into the distal portion of the anterior urethra. The entire anterior urethra appears normally patent, and the narrowed zone is no longer visualized. The external sphincter is visualized (arrow marked *E.S.*) and corresponds to its suspected location on the voiding urethrogram.

This, then, is another case of an anterior urethral valve which causes no obstruction to the retrograde flow of liquid but produces a fairly high degree of obstruction during voiding.

At cystoscopy, no valve could be seen while the cystoscope was passed retrograde into the urethra. After the bladder was distended with fluid and while the cystoscope was being withdrawn, at a point 2 cm. distal to the verumontanum, however, a flap of tissue slapped up against the end of the tube, obscuring the vision. This confirmed the presence of an anterior urethral valve.

Case 4. A 10-year-old Negro boy was examined because of a 3-year history of abdominal pain, frequency, and dysuria. Two years previously an intravenous urogram revealed bilaterally functioning urinary tracts with minimal changes in the upper calyces on the left indicative of infection.

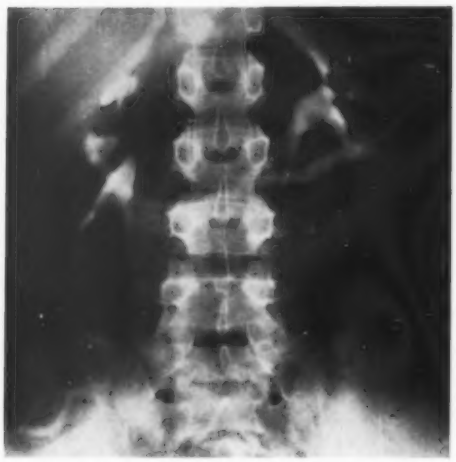


Fig. 3A. Case 3, a 12-year-old boy examined because of a persistent low-grade pyuria. Thirty-minute film of an intravenous urogram showing a rather severe dilatation of all the calices on the right side, indicative of pyelonephritis.

No voiding urethrogram was attempted. The child was placed on antibiotics, but the cultures remained positive. The current intravenous urogram again showed the minimal changes in the left kidney, but now a voiding urethrogram was added to the study.

Fig. 4 shows a narrowing of the most distal portion of the urethra. This narrowed zone was thought to be a stricture of the anterior urethra at the proximal end of the fossa navicularis. In actuality, as confirmed during the operation, the stricture is at the urethral meatus (arrow), and the narrowed irregular channel is formed by induration of the prepuce secondary to phimosis and chronic infection. The puddling of the dye is in a large preputial ulcer.*

DISCUSSION

There are many types of urethral lesions, both congenital and acquired, which can produce varying degrees of urinary obstruction in children. Since urinary excretion begins in the third month of intrauterine life, a tight posterior urethral valve producing almost complete obstruction has destroyed fetal kidney function before birth. If the obstruction is only partial, however, the child may be asymptomatic for years until infec-

*A report of Cases 2 and 3 has been accepted for publication by *Radiology* in an article entitled "Diagnosis of Anterior Urethral Valve by Voiding Urethrography: Report of Two Cases."

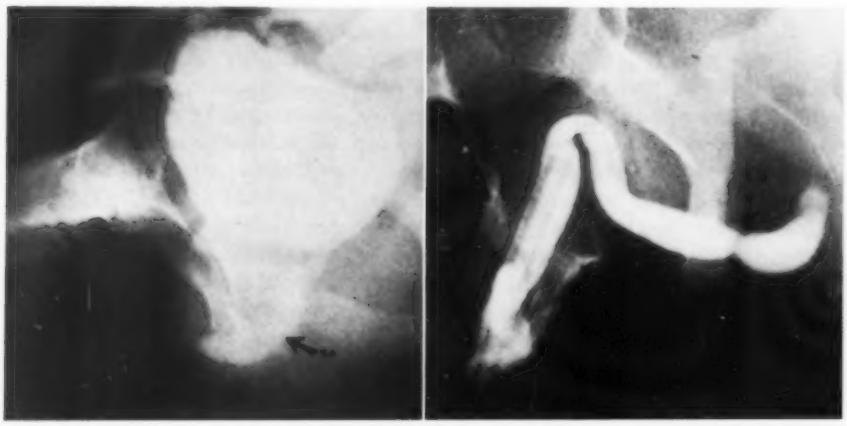


Fig. 3. *B*, Voiding urethrogram showing an abrupt narrowing of the stream in the anterior urethra (distal arrow). The proximal arrow is pointing to the external sphincter (*E.S.*). *C*, Retrograde urethrogram showing no stricture of the anterior urethra. The arrow points to the external sphincter *(E.S.)*. This retrograde study shows that the narrowing noted in Fig. 3, *B* occurs only while voiding.

tion supervenes. While the cause of most pyelonephritis in girls is unknown, in boys it is usually caused by some obstruction to urine flow. Frequently this obstruction is in the male urethra. Any procedure which can adequately demonstrate the male urethra is therefore of value.

Voiding urethrography during intravenous urography has been successful in a sufficient number of cases to justify it as a routine procedure in the male. We are not always successful with the infant or with the adolescent whose inhibitions prevent him from voiding. Environmental factors are very important. The lights of the room should be dim, with no one but the technician in the room with the patient. The doors should be closed and the patient assured that there will be no intrusion. If the child does not void within a relatively short period of time, he should be taken to the waiting room so that his bladder may distend further before another attempt is made. The carbonated beverage which was ingested at the beginning of the study also helps to distend the bladder. This second attempt is usually successful. We do not want to give the impression that this is always a simple procedure. As the study becomes routine, however, the technical problems gradually diminish and the diagnostic yield is great enough to justify the effort expended.

Fig. 4. Case 4, a 10-year-old Negro boy with a 3-year history of abdominal pain, frequency and dysuria, unresponsive to antibiotics. The voiding urethrogram demonstrates a narrowed irregular channel distal to the urethral meatus (arrow). This channel is formed by induration of the prepuce secondary to phimosis and chronic infection.

SUMMARY

1. The value of including a voiding urethrogram as a routine procedure during intravenous urography has been discussed.

2. Four cases illustrative of urethral lesions which could be corrected by operation have been presented.

3. Two of these 4 are, to our knowledge, the first cases of anterior urethral valves demonstrated in the United States.

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Escherichia freundii meningitis

Report of two cases

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PURULENT meningitis occurring in the neonate and in early infancy usually is caused by microorganisms which are normal inhabitants of the adult gastrointestinal tract. *Escherichia coli* has been cited as the most common etiological agent of meningitis in early infancy.[1, 2] Other gram-negative bacilli, such as *Friedländer's bacillus, Aerobacter aerogenes, Proteus vulgaris,* and *Pseudomonas aeruginosa,* have been isolated from the cerebrospinal fluid of infants with purulent meningitis.

Standard medical textbooks and the literature concerned with the cause of purulent meningitis in infancy and childhood do not mention *Escherichia freundii,* a separate and definite species in the genus Escherichia, as a causative agent of purulent meningitis. This is a report of two cases of infants with purulent meningitis in whom *E. freundii* was found to be the causative agent.

CASE REPORTS

Case 1. T. V., a 7-week-old white girl was admitted to the National Naval Medical Center because of recurrent convulsions occurring over a 3-day period. Pregnancy, labor, and delivery had not been complicated, and the patient had no unusual clinical problems in the first 4 weeks of life. When the patient was 4 weeks of age she developed twitching of the eyelids, stiffening of the body, and clonic movements of the extremities which lasted about 30 seconds. These spells occurred as often as 5 times a day and recurred daily. She became progressively lethargic and gained little weight.

Physical examination. The infant was pale and listless on admission; the weight was 4,500 grams, the length 22 inches, the head circumference 15¾ inches, and the fontanelle full. The pupils were equal in size and reacted equally to light and accommodation. The ocular fundi were normal. She cried with a high-pitched cry when unpleasantly stimulated and was noted to move all extremities. The deep and superficial reflexes were present and were of normal intensity for her age.

Laboratory studies. Hemoglobin level on admission was 12.5 Gm. per cent; the hematocrit determination was 38 per cent. The white cell count was 27,100, with a differential of 66 per cent polymorphonuclear leukocytes, 1 per cent band forms, 23 per cent lymphocytes, and 10 per cent monocytes. The roentgenogram of the skull

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The opinions or assertions contained in this article are the private ones of the writers and are not to be construed as official or as reflecting those of the Navy Department or the Naval Service at large.

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was unremarkable. The lumbar puncture showed the cerebrospinal fluid to be slightly cloudy and xanthochromic; a fibrinous web or pellicle was also noted. The total cell count was 2,930 per cubic millimeter; the majority of the cells were polymorphonuclear leukocytes. No organisms were noted. The protein level was 1,530 mg. per cent. A ventricular tap yielded a turbid fluid containing 38,000 white blood cells per cubic millimeter; 97 per cent of the cells counted were polymorphonuclear cells. The protein level was 2,400 mg. per cent and the chloride, 103 mEq. per liter. Gram stains made of the sediment of the ventricular fluid showed no organisms. Bilateral subdural puncture yielded less than 0.5 ml. of clear fluid on each side.

Escherichia freundii grew out on bacteriologic media from both the spinal and ventricular fluids. The organism tested by the disk method was found sensitive to tetracycline, chloramphenicol, sulfisoxazole, streptomycin, neomycin, and polymyxin B; it was resistant to penicillin, bacitracin, novobiocin, and erythromycin.

Hospital course. The patient was treated with sulfadiazine, 500 mg. per 24 hours, chloramphenicol, 500 mg. per 24 hours, and 4 million units of penicillin per 24 hours by the intravenous route. She also received 250 mg. of streptomycin per 24 hours intramuscularly. The intravenously administered antimicrobials were continued in the above dosages for 48 hours and then were administered intramuscularly. Penicillin was discontinued after the second day because the offending microorganism was found not to be sensitive to this drug. The hospital course was a stormy and protracted one. Fourteen days after the beginning of antibiotic therapy, a cisternal puncture yielded clear, sterile fluid.

All antibiotics were discontinued after 20 days of treatment. The white blood count returned to normal, but the patient continued to have frequent seizures, which were partially controlled by the administration of phenobarbital and Dilantin. She refused to suck and required feeding by gavage. A sixth nerve palsy was noted on the tenth hospital day. The head circumference had increased to 17⅛ inches 3 weeks after admission to the hospital. Six weeks after the onset of the illness, bilateral subdural taps were repeated with normal findings.

The neurological sequelae noted at 5 months of age were: generalized muscular rigidity, a sixth nerve paralysis, a high-pitched cry, and failure of mental and motor development. When discharged from the hospital at 6 months of age, the patient had developed hydrocephalus; the head circumference measured 18½ inches.

Case 2. J. L. was a 2-day-old premature white boy who weighed 2,250 grams at birth following an estimated gestation of 36 weeks. Labor lasted 12 hours and the delivery was performed hurriedly without the usual sterile technique or anesthesia; an episiotomy was not performed. The patient's mother developed a postpartum fever, which was thought to be the result of acute endometritis.

On the second day of life, the infant was found to have spells of apnea associated with cyanosis; he was then transferred to the U. S. Naval Hospital for diagnostic studies and evaluation. On admission to the hospital, the infant was jaundiced and had a rectal temperature of 103.2° F.; no other abnormalities were detected. Bacteriologic cultures from the umbilicus, as well as from the blood, revealed *E. freundii* sensitive to chloramphenicol and tetracycline but resistant to penicillin, sulfisoxazole, and streptomycin.

Hospital course. Penicillin, 300,000 units per 24 hours, and streptomycin, 150 mg. per 24 hours, were given intramuscularly, but on the second hospital day, because a gram-negative rod was isolated from the blood culture, the patient was treated with intravenous erythromycin, 200 mg. per 24 hours, chloramphenicol, 50 mg. per 24 hours, and penicillin, 500,000 units per 24 hours. Despite aggressive antibiotic therapy with these drugs, the infant died a day after admission.

Postmortem study demonstrated acute leptomeningitis, a massive abscess of the right cerebrum, and cloudy, turbid cerebro-

Table I. Differential bacteriologic characteristics of *E. freundii* and *E. coli*[9, 10]

Test	*E. freundii*	*E. coli*
Motility	Usually positive	Usually positive
Gelatin	Negative	Negative
H_2S	Positive	Usually negative
Methyl red	Positive	Positive
Citrate	Positive	Negative
Voges-Proskauer	Negative	Negative
Indol	Variable	Positive
Glucose	Fermented acid and gas	Fermented acid and gas
Lactose	Usually fermented	Usually fermented
Inositol	Usually not fermented	Not fermented

spinal fluid from which a pure culture of *E. freundii* was recovered.

DISCUSSION

Escherichia freundii is a species in the Escherichia genus characterized by its ability to utilize citric and citric acid salts as its sole source of hydrocarbon. It was first differentiated as a separate entity in 1928 by Braak[3] and named *Bacterium freundii.* In 1932, Werkman and Gillen[4] called this bacillus *Citrobacter freundii.* The specific name was given in honor of Freund, who in 1881 first observed that trimethyleneglycol was a product of fermentation of this microorganism. *E. freundii* occurs as short gram-negative rods, singly, in pairs, and in short chains, which may or may not be motile. *E. freundii* gives a negative Voges-Proskauer reaction. It is methyl red–positive, as in *E. coli;* but *E. freundii,* in contrast to *E. coli,* can utilize citric acid or citrate as its sole source of hydrocarbon, as does *A. aerogenes. E. freundii* can produce acid and gas from lactose; this microorganism also produces hydrogen sulfide in ferric citrate agar (Table I). *E. freundii* has been found in soil and water and, to varying degrees, in the intestinal tract of man and animals.

Many gram-negative rods have been identified as the causative agent of purulent meningitis in infancy and childhood. Most are normally occurring saprophytes: *E. coli, K. pneumoniae, A. aerogenes, Pr. vulgaris,* and *Ps. aeruginosa.*[5] Of these microorganisms the colon bacillus is considered by most observers to be the most frequent causative organism of meningitis in the infant[1, 7] Waite and Kline[8] have recently called attention to the pleomorphic microorganism, *Mima polymorpha,* which may occur as a gram-negative rod as another cause of meningitis in the pediatric age group.

It is curious that *E. freundii* has remained unmentioned in recent reviews of purulent meningitis in infancy.[7, 9] Whether this can be explained by the extreme rarity of its occurrence as a pathogen or by failure to detect its presence by incomplete fermentation and biochemical studies of gram-negative coliform organisms, which then are identified erroneously as *E. coli,* is open to conjecture. The latter explanation would seem the more likely. In the bacteriology laboratory at the National Naval Medical Center, where a battery of bacteriologic tests, including the citric acid utilization test, are performed on all coliform organisms, *E. freundii* is isolated occasionally from stool and throat cultures. This has been particularly true in patients who have received prolonged antibiotic therapy.

The practical significance of the fact that *E. freundii* can cause purulent meningitis in infancy remains to be evaluated. In the two cases we are reporting, the course of the illness, the antimicrobial sensitivities, and the eventual outcome did not differ from that usually seen in *E. coli* meningitis in infancy. We believe, however, that the routine use of the citrate test in the bacteriologic evaluation of coliform organisms may uncover additional cases of serious *E. freundii* infection. This, in turn, may reveal differences between these closely related microorganisms, not only in their response to antibiotics but also in the clinical course of the meningitis produced by each of these two related microorganisms.

SUMMARY

Two infants with meningitis caused by *E. freundii* are reported. To our knowledge,

this is the first report indicating that this microorganism may be sufficiently pathogenic to produce purulent meningitis.

The differential bacteriologic characteristics which distinguish *E. freundii* from the closely related *E. coli* are also described.

We wish to express our thanks to Dr. Philip R. Edwards, Chief, Enteric Bacteriology Unit of the Communicable Disease Center, Chamblee, Georgia, for his cooperation in this study.

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Craniofacial dysostosis, patent ductus arteriosus, hypertrichosis, hypoplasia of labia majora, dental and eye anomalies—a new syndrome?

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NUMEROUS cases of multiple congenital facial anomalies have been observed in which there are associated dental and alveolar abnormalities. These, in part only, have been recently grouped by McKenzie[1] into the "first arch syndrome." This partitioning has separated a heterogenous collection, which includes cleft lip and palate and the syndromes of Pierre Robin[2-6] (micrognathia, glossoptosis, and cleft palate), Treacher Collins–Franceschetti-Klein syndrome or mandibulofacial dysostosis[7, 8] (mandibular hypoplasia, macrostomia, abnormalities of external and middle ear, deafness, microphthalomos, sparse eyelash development, and antimongoloid obliquity of the palpebral fissures), and a host of other variations involving two or more associated signs,[9-14] such as the mandibular dysostosis of Nager-de Reynier[15] (macroglossia, defect of external ear), the hypertelorism of Greig and a similar syndrome described by Fisch and Renwick[16] (hypertelorism, different color of right and left eyes, congenital deafness, white forlock, and high palatal arch) which appears to be a forme fruste of Waardenburg syndrome.

Recently, the authors have had opportunity to examine 2 sisters who presented numerous identical congenital defects. Although the defects probably constitute a distinct, undescribed syndrome, we feel that there are

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certain similarities between these cases and other well-established syndromes that merit consideration.

CASE PRESENTATIONS

The patients were first seen on June 13, 1958. Because both presented almost identical anomalies, they will be described together. Their complaints were ulcers of the feet, fatigue, and facial anomaly.

G. G., a 10-year-old girl, weighed 53 pounds and was 50 inches tall, 1.5 and 1.7 standard deviations, respectively, below the norm for a girl of her age. Her 8-year-old sister, N. G., was 47 inches tall and weighed 43 pounds, both measurements being 1 standard deviation below the norm.

Present illness. Both girls had experienced painful ulceration near the metatarsal arch for 2 or 3 years. It was especially severe during winter, though it cleared up during warm weather. During routine examinations both girls were noted to have heart murmurs; fatigue had become more pronounced within the past few years. No cyanosis of dyspnea had ever been noted, however.

Family history. There were 3 male half-siblings by another father. They were 14, 16, and 18 years of age, and all were normal. The mother's brother was stated "to have a large head." No other relative was known to have any congenital anomaly and there was no parental consanguinity.

Past history. Both girls were full-term infants; both deliveries were uncomplicated. Development was noted to be "somewhat slow": they first sat at 10 months, walked at 19 months, and uttered their first words at 3 years. Their abnormal facial development was noted at birth and their defective vision, i.e., hyperopia, was diagnosed and treated by the age of 4 years. Bilateral frontal headache, though experienced by both, was more common in the elder girl.

The parents indicated that both girls were doing "about average" in school.

Physical examination. Examination revealed that both girls had similar congenital defects. Both were short but of stocky build. Both demonstrated mild anteflexion of the head during a walking gait. The "dished out" or saddled appearance of the upper face and depressed supraorbital ridges were more pronounced in the older girl (Figs. 1

Fig. 1. *A* and *B*, Frontal and lateral views of older sister, G. G., age 10. Note hypertrichosis, ectropion of lower lip, "dished out" appearance of middle face, anti-Mongoloid obliquity of palpebral fissures, and eyelid anomaly.

Fig. 2. *A* and *B*, Frontal and lateral views of younger sister, N. G., age 8. Marked overgrowth of scalp hair is evident. Lack of development of middle face is not as evident as in older sister.

and 2). Both had a pronounced amount of coarse scalp and body hair, especially on the arms, legs, and back (Fig. 3). A small amount of coarse pubic hair was noted in both children. The scalp hair line was lower than normal. Mild umbilical hernia was observed in both girls.

Eyes. Lid development was defective, resulting in the inability to open or close the eyes fully. Antimongoloid obliquity of the palpebral fissures could be noted, especially in the older child, as well as mild notching of the upper lids (Fig. 4). Scarring of the cornea with subsequent astigmatism was noted and thought to be secondary to improper closure. Hyperopia (20/400) was marked and considered primarily due to small globes, or microphthalmia. Reaction to light was normal, but accommodation was poor. Horizontal nystagmus was noted during an extreme lateral gaze, and the upper gaze was extremely limited. No lens abnormality was observed. The younger girl demonstrated congenital remnants of the pupillary membrane in the right eye.

Ears. The pinna was essentially normal with a somewhat prominent preauricular fold. Narrow external orifices were noted. Mild bilateral conduction loss was noted in both girls.

Mouth. Because of the severe dysostosis of the maxilla, zygoma, and nasal bones, especially in the elder child, a Class III molar relationship was present. In addition, a high-arched, narrow palate, in combination with a decrease in the number of teeth, provided poor masticating function. The maxillary tuberosities were unusually prominent. The soft palate was small. Loss of vertical height due to abnormally positioned dentition and faulty occlusion produced some ectropion of the lower lip. Several teeth exhibited microdontia. The lower incisors had well-developed mamelons due to failure of attrition. Distobuccal cusps were missing on the lower first permanent molars. The height of the body of the mandible was moderately reduced in the middle third.

In the younger girl, all 4 primary second molars were congenitally missing, and in the

permanent dentition all second bicuspids and upper first bicuspids were congenitally absent. In the case of the older girl, 3 permanent first molars, all permanent second and third molars, mandibular second bicuspids, and all maxillary permanent bicuspids were missing.

In both children the crowns of the teeth were bell shaped with short, spindle-shaped roots (Fig. 5). The pulp chambers were small or missing in some teeth. Some unerupted permanent teeth were vertically oriented and a large distance separated them from their resorbing predecessors. Carious lesions were conspicuously absent.

Cardiac anomaly. Grade III and IV "machinery-like" murmurs were noted in the elder and younger girl, respectively. Thrills, loudest at the 2 to 3 intercostal space, were interpreted as patent ductus arteriosus. Surgical examination confirmed this opinion, and repair with essentially uneventful recovery followed.

Laboratory findings. Blood urea nitrogen, carbon dioxide combining power, chloride, phosphate, sodium, potassium, cholesterol, alkaline phosphatase, and protein-bound iodine were all found to be normal.

Genital examination. Both girls had extreme hypoplasia of the labia majora, the fourchette gaping widely (Fig. 6). The vaginal and urethral orifices were normal, however.

Roentgenographic examination. The sisters demonstrated differing degrees of similar malformations of the neuro- and splanchnocranium, including premature synostosis of the coronal suture, lordosis of the petrous ridges, absolute clival hypoplasia, elevation of the lesser sphenoidal wings, brachycephaly, and relative ocular hypertelorism. The maxillary and nasal bones were underdeveloped with some asymmetric development of the sphenoid. These changes led to a *general* diagnosis of craniofacial dysostosis (Figs. 7 and 8).

Analysis was carried out by methods previously described in detail by Moss and co-workers[17-21] in several papers. It is quite evident that neither girl presented all of the signs characteristic of solitary premature synostosis of the coronal suture.[21] The characteristic clival hypoplasia, however, was evident in both cases.

Fig. 3. Hirsutism of older girl. Marked lanugo hypertrichosis extends to involve face.

Fig. 4. Defective upper eyelid development of older girl. Note notch at arrow.

In general, the older girl was more severely deformed. Her posterior cerebral fossa was more deeply situated, with consequent alteration in the plane of the foramen magnum. This plane extended obliquely downward and backward, instead of being identical with the plane of the hard palate.[22] A marked basal kyphosis was also apparent. There was reason to suspect that this was due to secondary "postural flattening" superimposed on the unilateral coronal synostosis. The splanchnocranium was also more severely deformed, presenting a most unusual sinuosity of the hard palate.

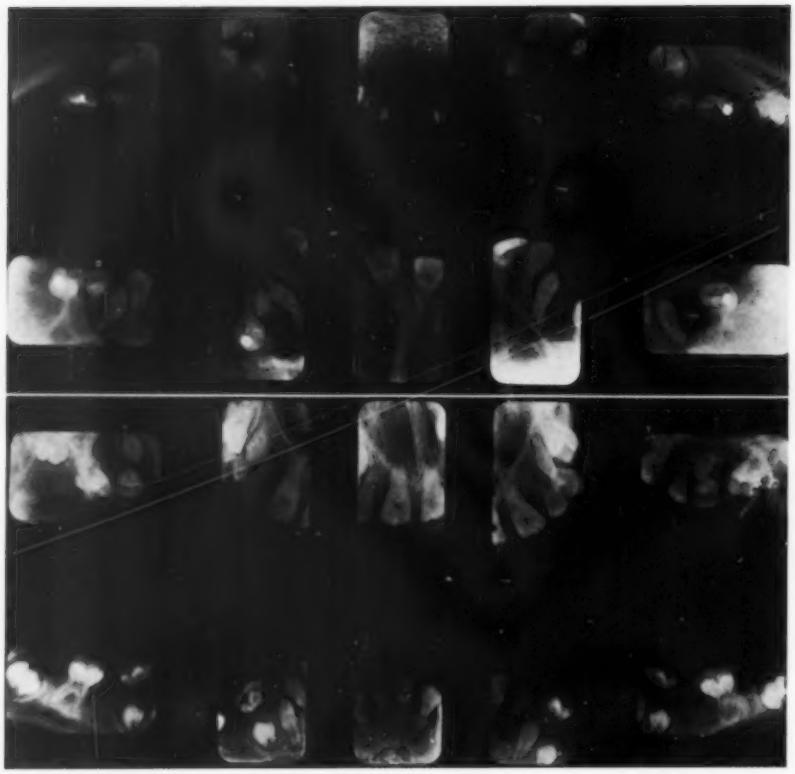


Fig. 5. *A* and *B*, Dental roentgenograms of G. G., age 10, and N. G., age 8, respectively. Note widespread diastemas, congenitally missing teeth, malformed unerupted permanent teeth, cervical constriction of mandibular incisors, and diminution of pulp chambers and canals.

DISCUSSION

Etiologically, the petrous lordosis, the basal kyphosis, and the shifting of the foramen magnum are secondary mechanical results of an alteration in the direction of growth of the brain brought about by the other primary basal congenital malformations.

These two girls can be compared in many respects with those described as having the Treacher Collins–Franceschetti-Klein syndrome. In this syndrome there is hypoplasia of the malar bones and mandible. Malformation of the external and internal ear and deafness are common in the "first arch syndrome." Hearing was somewhat reduced in both girls and narrow external orifices were noted, especially in the older girl.

High palate and abnormal position and occlusion of the teeth are also common to both disorders. On the other hand, neither sister exhibited macrostomia nor were blind fistulas present between the angle of the mouth and ear as seen in the Treacher Collins syndrome. Although both sisters exhibited hirsutism, profuse hair growth in the form of tongue-shaped processes extending to the cheeks was not noted. Both girls had eyelid anomalies, the older sister demonstrating the anti-Mongoloid obliquity of the palpebral fissures particularly well. Notching was also noted in this sister. In addition, both girls seemed to have "incomplete lid development," i.e., there was not enough lid to completely cover the eye, which produced

Fig. 6. *A* and *B*, Genital area of G. G. and N. G., respectively. Note lack of development of labia majora with gaping fourchette. Pubic hair development, present in both, was marked in older girl.

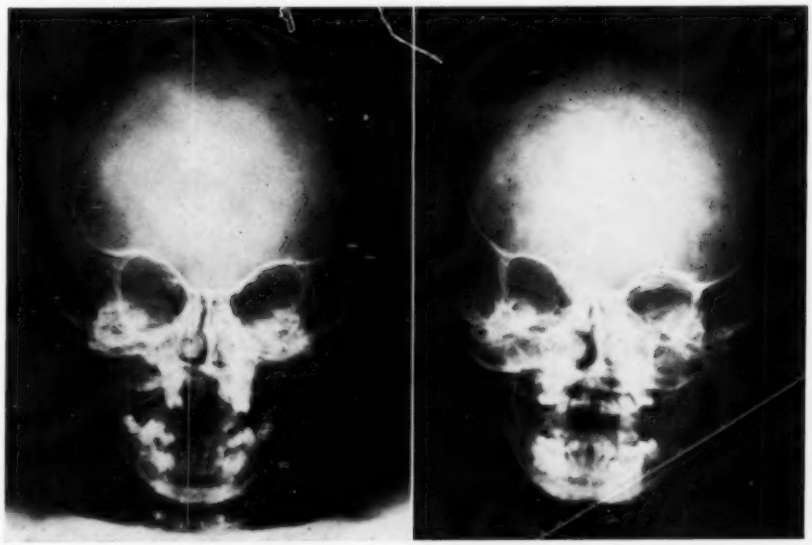


Fig. 7. *A* and *B*, Roentgenograms of N. G. and G. G., respectively. Both sisters show similar malformations of neuro- and splanchnocranium. Brachycephaly, relative ocular hypertelorism, maxillary and nasal bone underdevelopment, and some asymmetric development of sphenoid are evident.

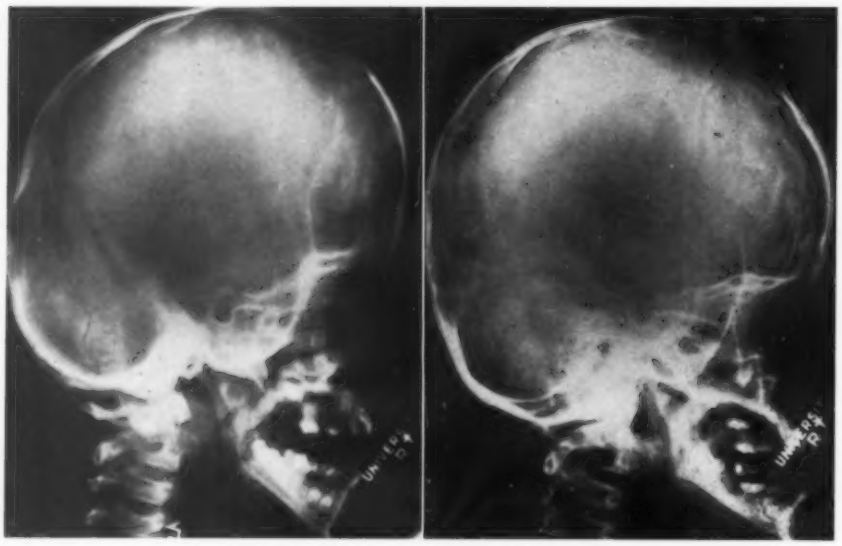
secondary corneal opacity. Both had essentially normal mental development as demonstrated by clinical testing of their intelligence quotients.

The dental anomaly was most unusual. The teeth, on purely external appearance, were somewhat translucent and gray, not unlike those seen in dentinogenesis inperfecta. The teeth in this latter condition characteristically do not have root chambers and canals and have narrow tapering roots with cervical constriction. Examinations of their dental roentgenograms reveal some root constriction, especially of the lower incisors. Root canals were present but somewhat diminished in width.

Congenital absence of teeth was marked in both girls. Böök,[23] in 1950, reviewed hypodontia and proposed a new symptom complex designated as the PHC syndrome which included premolar hypodontia, hyperhidrosis of the palms and soles, and canities or premature whitening of the hair. Neither excessive sweating nor canities was seen in our cases. White forelock is seen in the Fisch-Renwick[16] and Waardenburg[25] syndromes. Cotterman and Falls[24] also observed white forelock in Bonnevie-Ullrich syndrome as well as microdontia. Hypodontia has been cited as being present in the Franceschetti-Klein syndrome,[8] and many of the oral and facial anomalies in these sisters seem to be compatible with that diagnosis.

Although in these two cases we appear to be dealing with a symptom complex that would include the "first arch syndrome," we question the wisdom of grouping a large number of etiologically different conditions under the anatomical location in which the developmental error has occurred. By analogy, little would be added if "all malformations of the lower limbs were grouped as the 'lumbar myotome syndrome.' "[26]

From these two cases it is impossible to ascertain whether all the anomalies observed could be predicated upon a single pleiotropic gene or multiple, closely linked, genes. A single gene can produce any combination of signs and symptoms, the limits being the specificity of the chemical reaction involved,



A *B*

Fig. 8. *A* and *B*, Lateral view of N. G. and G. G., respectively. Note premature synostosis of coronal sutures, lordosis of petrous ridges, abnormal clival hypoplasia, and elevation of lesser sphenoidal wings.

its time of action, and the states of differentiation of the cells, tissues, or organs involved.

SUMMARY

Two cases are described which present craniofacial dysostosis, patent ductus arteriosus, hypoplasia of the labia majora, and dental anomalies. The relationship of the new syndrome to that of other well-recognized symptom complexes and the dubious value of grouping a large number of etiologically different conditions under the "first arch syndrome" are discussed.

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Sudden unexpected death in infancy

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IN RECENT years there has been increasing interest in sudden unexpected deaths of infants due to the striking rise in the number of such deaths relative to total infant mortality. Stowens[1, 2] states that 16 per cent of the deaths of infants 1 to 6 months of age upon whom autopsies have been performed and 4 per cent of the total pediatric cases in the Armed Forces Institute of Pathology now fall into this category. Reports from Germany, England, Australia, and Canada reveal this to be a world-wide problem. In the published studies of these cases there are, however, many divergent views as to the cause of the fatalities, among which may be listed status thymicolymphaticus, smothering, overwhelming upper respiratory infection, allergic reactions, and generalized neurospasm.

A group of infant deaths occurring within a short time early in 1958 stimulated the study of these cases as they involved the greater metropolitan area of Minneapolis, Minnesota. We were interested in determining the magnitude of the problem in our population and in discovering any facts that would tend to resolve the conflicting views as to the cause of these unexpected deaths.

MATERIAL

The present study is based on all cases of sudden unexpected death in infants, 5 days to 1 year of age, reported to the Hennepin County coroner between Jan. 1, 1958, and June 30, 1959. There were 84 such deaths comprising 10 per cent of the infant mortality for this period. We feel this percentage to be actually lower than the true incidence since the total infant mortality for Hennepin County is increased by deaths in the metropolitan hospitals of patients referred from all over the state. The age and sex distributions of the group studied are given in Fig. 1. Males comprised 56 per cent of the total group; the average age was 2.8 months. Four of the group were Negroes. The infants came from all strata of society, including the homes of professional people and unemployed workers, and were distributed throughout the area with the majority of deaths occurring within the city limits of Minneapolis. In only a single instance had a similar type of death occurred in a family previously. The group included 3 sets of twins of which 1 sibling of each died. A seasonal variation was noted with the highest number occurring during the spring months in both years and a second peak occurring in December, 1958.

Study of this series was divided into 3 major inquiries: (1) an epidemiologic survey, (2) postmortem laboratory studies, and (3) a study of the anatomic pathologic condition.

EPIDEMIOLOGIC STUDIES

Following the original investigation by the coroner or his deputies, 76 of the cases were studied further by the Minneapolis Health Department under the direction of E. E. H. Public health nurses from the city

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and rural county visited the homes to investigate the infant environs and to question the parents when they had recovered from the initial shock of the death. Specific information was obtained on the circumstances of the death, and detailed medical histories were elicited for the infants, the families, and other persons in the household.

The majority of the infants came from families with 1 to 3 other children (64.5 per cent) and from homes that were good or modest but adequate (86.8 per cent). In only 8 cases could the sanitation in the home, including drinking water, sewage, and general cleanliness, be considered poor. Thus crowding, poor housing, and/or lack of sanitation could not be considered important contributing factors in these deaths.

Forty-six per cent of the infants had received routine medical examinations for health supervision from a few hours to 1 month prior to death. Clinical findings were normal in 2 infants seen a few hours prior to death. Ten per cent of the infants on whom information about feeding was obtained had been breast fed.

All of the deaths were not actually sudden and unexpected. In 3 the family physician had been consulted by telephone, and 2 of the infants had been seen by a physician within 24 hours of death because of symptoms of illness. In the remainder, the initial stories generally were similar. The infants had been placed in bed apparently normal and were found moribund (3 cases) or dead one to several hours later. Detailed histories, however, frequently revealed some abnormality to be present in infant, family, or both (see Table I).

Symptoms of illness were found in 72.4 per cent of the infants. Upper respiratory infection was most frequently noted, with 40 (52.7 per cent) manifesting evidence of runny nose, cough or, "flu" in the infants, family, or both. Associated symptoms in some of the infants were fever, restlessness, and increased somnolence.

Gastrointestinal symptoms were the second most common, with diarrhea, vomiting, or both being manifest in the deceased infant and/or family in 9 (11.9 per cent). Additional symptoms in these infants were fever, loss of appetite, increased somnolence, and irritability.

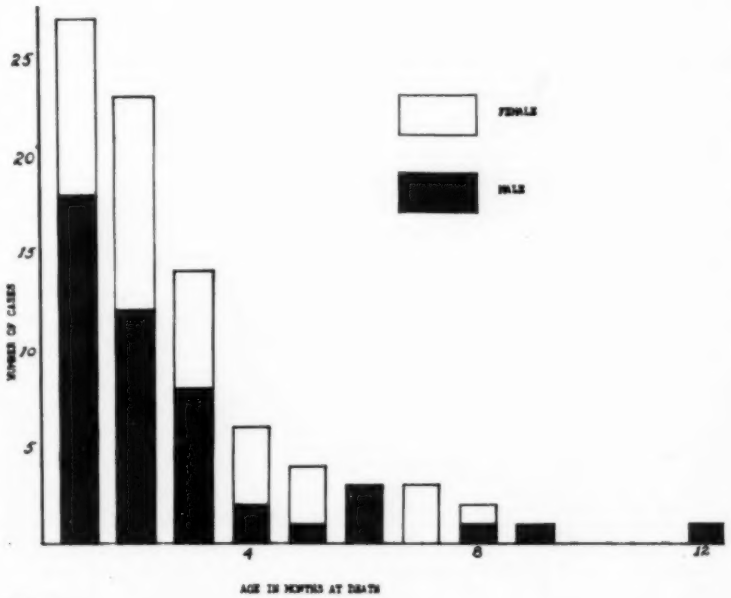

Fig. 1.

Table I. Main symptoms of illness by type

Type	*Number*				*Per cent*
	Infant	*Family*	*Both*	*Totals*	
Respiratory	17	7	16	40	52.7
Gastrointestinal	3	1	5	9	11.9
Increased irritability	2			2	2.6
Severely undernourished	1			1	1.3
Other	3			3	3.9
None				21	27.6
Totals				76	100.0

Two infants, aged 5 days and 30 days, were found dead on the same morning following a hot 93° F. summer night. Their only symptom was increased irritability.

One of the interesting facts evolving from the study was the high incidence of prematurity. Twelve of the 76 infants had been born before term (15.8 per cent), as compared to 6 per cent in the community. Other perinatal abnormalities were breathing difficulty and cyanosis in a 26-day-old, full-term infant who had been under close observation since birth, cleft palate in a 3-month-old infant, absence of the left kidney in a 12-month-old infant, mental deficiency with convulsions in a 7½-month-old infant, and multiple abnormalities in a 3-month-old infant whose mother had German measles in the second month of pregnancy.

Smothering was felt to be a factor in only 3 cases. The head of a 1½-month-old infant was wedged between the rails of the crib with the face against the mattress. A 9½-month-old infant had fallen between the crib and the partially unfastened side of the crib with his throat and face wedged against spring and mattress. Autopsies were not done on these 2 infants. In the third, a plastic bag was found on the face of a 7½-month-old infant.

A check was made for vomiting and bowel movement near the time of death. Only 7 instances of vomiting and 2 of a large evacuation were noted in the series.

LABORATORY STUDIES

Bacteriologic examinations were done on 19 of the infants early in the series with cultures of the lungs and/or blood. In only 2 were pneumococci isolated from the lungs and these infants showed definite bronchopneumonia. In a third infant beta hemolytic streptococci were found in both lungs and blood. The majority of organisms isolated, however, were those which usually are not pathogens, such as *Streptococcus viridans*, *Staphylococcus albus*, paracolon bacillus, Aerobacter, Pseudomonas, and *Escherichia coli*. Their presence bore no recognizable relation to the anatomic pathologic condition. No organisms were found in lung cultures from 2 infants having prominent pneumonia, and a variety of organisms, including hemolytic *Staphylococcus aureus*, was obtained from many of the lungs showing no inflammatory reaction. Bacteriologic studies undoubtedly would have been helpful in some of the later cases, such as in the infants with Waterhouse-Friderichsen syndrome and in the infant with acute enteritis.

Viral studies on pulmonary tissue were even less rewarding. In 15 infants isolation of a virus from lung tissue was attempted by intraperitoneal and intracerebral inoculations into infant mice and adult mice. Embryonated eggs were inoculated as well as HeLa cells, monkey kidney, and amnion tissue culture tubes. No virus was found.

Fractionation of serum protein was performed on postmortem blood from 12 of the younger infants to determine if gamma globulin was reduced significantly. Total protein was determined by the biuret reaction and fractionation by paper electrophoresis. The results of this study are given in Table II. It will be noted that all cases fall within

Table II

Age (months)	*Sex*	*Gamma globulin (mg. %)*	*Principal findings at autopsy*
1/6	F	1420	Waterhouse-Friderichsen syndrome
2	F	876	Bronchopneumonia
3	F	720	Bronchopneumonia
3	M	730	Laryngotracheobronchitis
3	M	564	Laryngotracheobronchitis
2	M	455	Questionable pneumonia
2	M	840	Questionable pneumonia
1	M	780	Pulmonary congestion and edema
1	M	360	Pulmonary congestion and edema
2	M	730	Pulmonary congestion and edema
5	M	480	Pulmonary congestion and edema
3	F	490	Congenital heart disease, Mongolism

the normal range obtained by this method and are independent of the anatomic pathologic condition observed.

ANATOMIC PATHOLOGY

Seventy-eight autopsies were performed which included complete examination of all the viscera, the organs of the neck, and the brain. Sections were taken from all 5 lobes of the lungs in all cases. The sinuses, mastoids, middle ears, and spinal cords were examined in some cases, but this was not part of the routine. The time between death and autopsy varied from minutes to hours but was never more than 1 day. Sections from all organs were stained routinely with hematoxylin and eosin. Special stains were used when indicated. On the basis of the anatomic pathologic findings, the series can be broken into 3 groups.

Group A. This group consisted of 34 patients (44 per cent of the total series at autopsy) in whom a gross or microscopic pathologic condition was prominent and considered to be the cause of death. The principal finding in each of this group is listed in Table III.

It will be noted that the great majority of the group had respiratory infections. In determining the infants to be included in Group A, only those showing prominent and acute inflammatory reactions were considered. The presence of lymphocytes in any portion of the respiratory tract, no matter how prominent, was not considered of significance unless accompanied by neutrophils. An example of the respiratory lesions felt to be significant is shown in Fig. 2.

The age of the infants in this group varied from 1 to 12 months with an average of 4.0 months. If only the infants with respiratory infection are considered, the average age was 3.8 months.

Group B. This group consisted of 22 infants (28 per cent of the series at autopsy) in whom the anatomic pathologic condition was considered equivocal for pneumonia. In all of these a questionable inflammation of the respiratory tract represented the only pathologic condition found. In 3 there was definite thickening of interalveolar septa but no acute inflammatory cells and relatively few lymphocytes either in the thickened septa or in the alveolar spaces. A representative field is shown in Fig. 3.

The remaining 19 infants in this group were those in whom the microscopic examination of the lungs revealed not only con-

Table III

Principal findings at autopsy	*Cases*
Bronchopneumonia	19
Laryngotracheobronchitis	7
Waterhouse-Friderichsen syndrome	3
Streptococcal septicemia	1
Idiopathic myocarditis	1
Acute enteritis	1
Pyelonephritis	1
Congenital heart disease	1

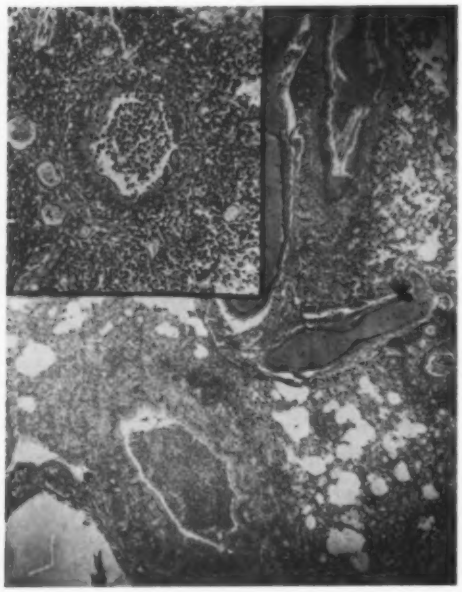

Fig. 2. A-58-1473, 7-month-old girl. No symptoms prior to death. Note severe acute inflammatory reaction in bronchi and surrounding lung tissue. (Low power ×40, inset, ×100; reduced approximately ¼.)

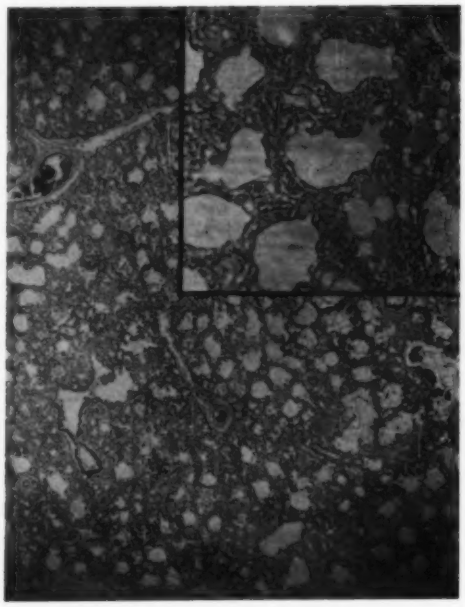

Fig. 3. A-58-2271, 1-month-old girl. No antemortem symptomatology. Interalveolar septa are thickened and contain a few lymphocytes. Some alveoli are lined in part by a thin proteinaceous membrane. (Low power ×40, inset, ×100; reduced approximately ¼.)

gestion of the interalveolar capillaries but also the presence of numerous neutrophils in these vessels (Fig. 4). This vascular concentration of leukocytes was limited to the lungs in each case. Occasional polymorphonuclear leukocytes had escaped into the alveoli in widely scattered spots. The histology was similar to that described by Orrahood[3] for septal pneumonia but with neutrophils rather than lymphocytes being the prominent cells in the capillaries. The authors felt this pathologic finding to be suggestive of a very early inflammatory reaction with beginning margination of the neutrophils.

The age of infants at death in Group B varied from 1 to 4 months with an average of 2.3 months.

Group C. This group consisted of 22 infants (28 per cent of the autopsied series) in whom no anatomic pathologic condition was present in sufficient degree to be considered the cause of death. In this entire group the lungs showed varying degrees of congestion and edema but no evidence of acute inflammation (Fig. 5). In the bronchi and trachea of many infants clusters of lymphocytes were noted in the submucosa, but these were not considered significant.

In 3 of the infants small areas of inflammation were seen in the larynx, characterized by small areas of fibrinoid degeneration in the submucosa of the vocal cord lying beneath an intact epithelium and showing an infiltration of a few neutrophils and Anitschkow cells about the area of degeneration (Fig. 6). These lesions were identical with those which have been described by Adelson[4] and Valdes-Dapena.[5]

The age of the infants in this group varied from 1 to 5 months with an average of 1.5 months.

A common pulmonary finding was the presence of macrophages in the alveolar edema fluid. These were present in infants showing definite acute inflammation, ques-

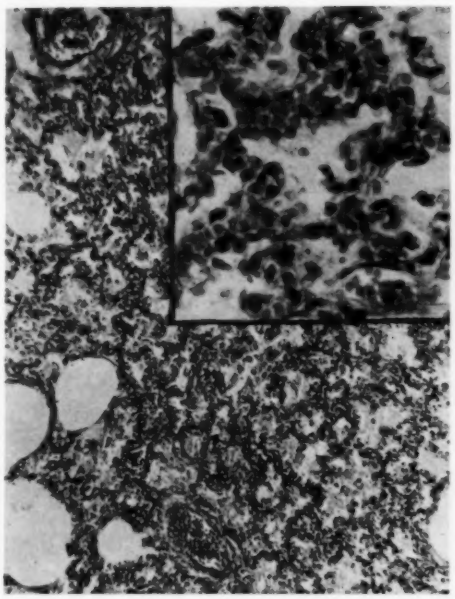

Fig. 4. A-59-1880, 2-month-old girl. History of a "cold" for 2 days. Note cellular appearance of septal capillaries and the presence of numerous neutrophils within the capillaries. (Low power ×100, inset, ×380; reduced approximately ¼.)

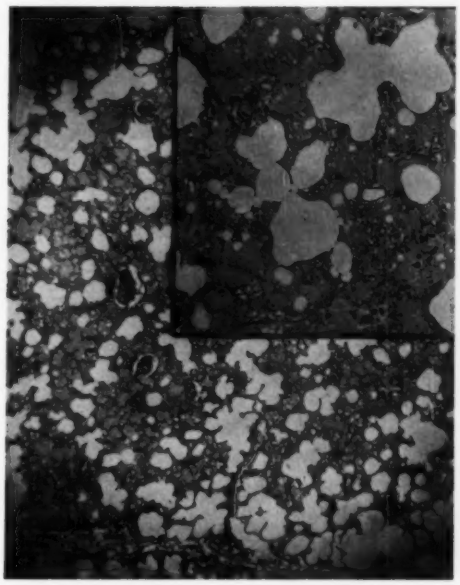

Fig. 5. A-58-2643, 1-month-old boy. No symptoms prior to demise. The lung shows pulmonary congestion and edema with some alveolar spaces containing macrophages. (Low power ×40, high, ×100; reduced approximately ¼.)

tionable pneumonia, and no inflammatory change. As far as can be determined, this mononuclear infiltrate is identical with that described by Gruenwald and Jacobi.[6]

No consistent or prominent abnormality was found in the lymphoid tissue. Thymus glands showed variation in size, but the larger ones were distributed throughout all 3 groups in equal proportion and the largest gland weighed only 35 grams. Visceral lymph nodes, particularly those in the mesentery, showed considerable variation in size, but again the infants having more prominent nodes were distributed throughout all groups in equal proportion. In 2 of the infants with moderate mesenteric adenitis, the germinal centers of the nodes showed tiny areas of necrobiosis. In the other enlarged glands the changes were simply those of hyperplasia.

Five infants who had died violently during this period served as a control group. A homicidal shooting, a homicidal drowning, an accidental drowning, and 2 strangulations had brought death to these infants at 1 to 4 months of age. In 4 of these 5, the lungs showed pulmonary congestion and edema with mild lymphocytic and macrophage infiltration of the alveoli. No evidence of other abnormality was found in the respiratory tract.

DISCUSSION

The material in this series is similar to that in other reported groups. In most series, 80 per cent or more of the deaths have occurred in the first 6 months of life, with the median age varying from 2.5 to 3.5 months and with the peak incidence at the first or second month. In all series males have been predominant, the range being from 55 per cent as reported by Adelson[4] to 75 per cent as reported by Rabson.[7] Some divergence is noted between the reported groups in relation to racial incidence with Adelson,[4] Valdes-Dapena,[5] and Rabson[7] reporting larger numbers of Negro infants than would

be expected from the proportion of Negro population in the areas from which their groups were drawn. Stowens[1, 2] found no disproportionate number of Negroes and none was evident in our own series. Investigators[4, 8, 9] making epidemiologic studies have obtained similar results to our own with frequent symptoms of upper respiratory infection noted either in the infants or in their families. The incidence of prematurity was elevated in some groups including our own and not in others.[1, 2, 4]

Despite the essential similarity of material there is wide divergence of opinion as to the cause of death in the majority of such infants due in part to the inability to find a definite etiologic agent. The findings of other investigators[1, 2, 4, 8, 9, 10] parallel our own in bacteriologic and virologic studies.

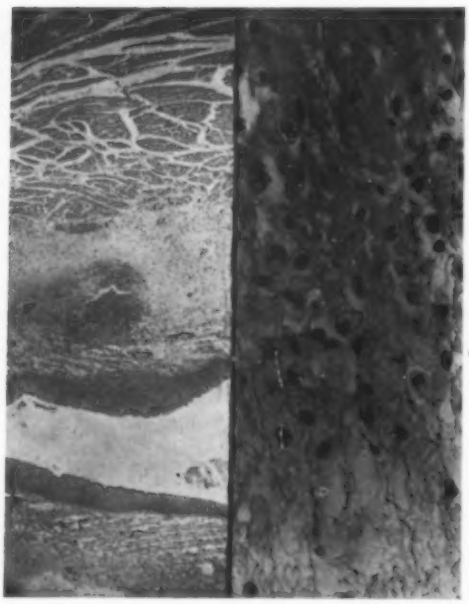

Fig. 6. A-59-1687, 1-month-old boy. No symptoms prior to death. There is a small area of fibrinoid degeneration in the submucosa of the larynx under an intact epithelium. A small number of neutrophils and Anitschkow cells are found at the edge of the necrosis. (Low power ×40, high, ×380; reduced approximately ¼.)

In only a very few cases can a definite organism be implicated.

A commonly accepted mode of death early in the century was smothering. Although the concept retains a few adherents, such as Carr,[11] it generally has been discarded on the basis of more complete autopsies, the observation of many of these babies at the time of death,[4, 9] and the experimental studies of Woolley.[12] Similarly, the recognition of the marked variation in the prominence of the lymphoid tissue which exists among infants and children[7, 13, 14] has caused the concept of status thymicolymphaticus to be abandoned with the possible exception of the very rare case where an enlarged thymus had been thought to produce mechanical obstruction to the airway.[15, 16]

In recent years emphasis has been given to more careful postmortem examinations. As a result, a large number of anatomic lesions have been described to account for some of the unexpected deaths. Among these may be listed congenital heart disease,[1, 2, 4, 9, 13] subendocardial fibroelastosis,[17] primary[18, 19, 20] and secondary myocarditis,[21] pyelonephritis,[22] encephalitis,[1, 2] septicemia,[23] primary virus pneumonitis,[24] cytomegalic inclusion disease,[2] adrenal hypoplasia, [2, 15] bronchopneumonia, and laryngotracheobronchitis.[4, 7-10, 14, 25-28] Such definite causes account for 15 to 80 per cent of the deaths in various reports.

In all large groups there are a number of patients with none of the causes listed above but showing varying degrees of change in the respiratory tract. Frequently the pathologic condition is minimal and the interpretation of these changes has varied among the observers.

Gruenwald and Jacobi[6] in 1951 described a mononuclear pneumonia in 47 infants who died suddenly and unexpectedly. Their description of this process consisted of a hemorrhagic pulmonary edema with an infiltrate of lymphocytes and macrophages into the alveoli. It was felt to be a specific pathologic picture. Other investigators,[29] however, have found similar pulmonary changes in infants dying after violence. In our own control group identical pulmonary histology was

noted in 4 of the 5 cases. Thus both the specificity and significance of such findings are open to question.

A number of investigators have noted minors changes of inflammation in the upper respiratory tract or lungs which have been interpreted by some as indicative of an overwhelming respiratory infection[8, 9] and by others as due to an allergic or hyperimmune reaction.[5] Stowens,[1, 2] in contrast, disregards these minor changes as within normal limits for an infant. He advances the theory that, because of cerebral immaturity, the cortex does not inhibit the reticular center and a viscerovisceral reflex causes pulmonary edema and death. As supporting evidence he found in 700 such cases on file in the Armed Forces Institute of Pathology that one-half of the infants had vomited and one-fourth had massive bowel movements at the time of demise. Our own series lends no support to Stowens' theory, with less than 11 per cent of our 84 infants having either large bowel movement or regurgitation near the time of death.

The division of the respiratory pathologic conditions presented here seems, at present, unique, with no previous investigator segregating a group of questionable pneumonias characterized by neutrophilic congestion of the pulmonary capillaries. Whether the concept of these as early pneumonias is valid, it leads to the interesting observation that the anatomic pathologic findings in the lungs were related to the age of the infants at death. The group showing definite anatomic inflammatory lesions of the lung (Group A) had an average age of 3.8 months, those with questionable early pneumonia (Group B) an average age of 2.3 months, and those showing only minor changes (Group C) 1.5 months. We cannot find this correlation previously stated. The closest similar observation is that of Stowens to the effect that death in infants over 6 months of age was usually due to a specific disease.

While such an observation does not help in determining an etiologic agent or the exact mechanism of death, it does lend support to the theory that death in most of these infants is due to respiratory infections in which the age of the patient will determine in large measure the anatomic pathologic condition found at autopsy. It is felt that in many of the younger infants showing only pulmonary congestion and edema, we are dealing with a preinflammatory state in which death occurs before recognizable inflammatory lesions can develop. In this younger group there is known to be less ability to combat infections and an increased sensitivity to nervous stimuli. Although we did not find the low gamma globulin values reported by Spain,[30] other experimental work[31] has revealed decreased bacteriostatic activity of the plasma in infants 1 to 2 months of age. Furthermore, in our series, as in others, there was a definite seasonal occurrence of these deaths which corresponds to the incidence of upper respiratory infections in the general population.

No criteria by which physicians could anticipate these sudden deaths were evident in the clinical histories or laboratory results obtained.

SUMMARY

1. Sudden unexpected death accounted for 10 per cent of the infant mortality in the metropolitan area of Minneapolis, Minnesota, from Jan. 1, 1958, through June 30, 1959.

2. Eighty-five per cent of the deaths occurred before 6 months of age, with the average age 2.8 months and the peak incidence in the first month of life.

3. Careful inquiry into the circumstances surrounding the deaths revealed no significant factors in regard to race, socioeconomic status, or heredity. There was an increased number of premature infants in the group (16 per cent) and symptoms of upper respiratory infection in the infants or their families were noted in 53 per cent.

4. Bacteriologic and virologic studies were of value in only a small percentage of the cases.

5. Careful postmortem examinations revealed a definite cause of death in 44 per cent of the cases, questionable early pneu-

monia in 28 per cent, and no distinctive pathologic lesion in the remaining 28 per cent.

6. On the basis of acute inflammatory changes in the respiratory tract, the series could be divided into 3 groups. Those with definite acute laryngotracheobronchitis or pneumonia had an average age of 3.8 months, those with questionable pneumonia an average age of 2.3 months, and those with no acute inflammatory changes an average age of 1.5 months.

7. On the basis of the age differential between the three groups, it is felt that most of these infants died as a result of respiratory infections in which the age at the time of death determined in large measure the anatomic pathologic findings at autopsy.

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Isolated palatal paralysis

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DEFECTS of speech are common in children but the mechanisms of their production are frequently poorly understood. It is the purpose of this paper to present 3 cases in which defects of speech similar to those associated with clefts of the palate were caused by a paralysis of the palate. The paralysis was unassociated with other obvious neuromuscular weakness and hence we have termed this condition "isolated palatal paralysis." It is presumed that the defect is of congenital origin.

All of the children are patients in the Cleft Palate Clinic of St. Christopher's Hospital for Children. The diagnosis was made by direct observation of the palate during phonation and by roentgenographic technique of cinefluorography which permits rapid motion picture exposures.[1]

A review of the literature has revealed only 1 reported case of an isolated, congenital paralysis of the palate, although other authors have made reference to the existence of this entity. In the case described by Moore and colleagues[2] the palatal paralysis was considered to be the result of a lesion in the corticobulbar tract. In 1938 Vernieuwe[3] described isolated palatal paralysis resulting from a variety of etiologic agents and mentioned, without description, a congenital palatal insufficiency. Froeschels and associates[4] state that hypernasality of speech may occur from many causes, among which are "congenital or acquired shortness and/or immobility of the soft palate."

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CLINICAL DESCRIPTION

Initial signs of the palatal paralyses were manifested shortly after birth by regurgitation of milk through the nares during feeding. Despite the regurgitation, the infants gained well and otherwise appeared healthy.

The second manifestation appeared when the children began to speak. Speech from the onset was hypernasal and unintelligible. The age at which words were first attempted appeared unrelated to the palatal defect.

The significant physical findings at the time of our examinations were confined to the palates, 2 of which were of normal configuration and 1 of which was slightly foreshortened. There was no change in the color or texture of the palates suggestive of submucous clefts. The uvulae were in the midline and normal in appearance. Motion of the palate during phonation was completely absent in 1 case and minimal in 2. The minimal movements noted were symmetrical.

There was no excessive drooling or any disturbance of the gag reflexes.

Numerous diagnoses had been offered for the disturbances of speech and feeding, but in no instance had a paralysis of the palate been suspected before the age of 6 years. In 2 cases, the correct diagnosis was made by dentists.

CASE REPORTS

Case 1. M. P., an 11-year-old white girl, was born to a gravida i, para i, 18-year-old, Rh-negative female after an uneventful pregnancy. Delivery was spontaneous. The neonatal period was complicated by mild diarrhea. Shortly after birth it was noted that the infant regurgitated milk feedings through the nares.

Development was apparently normal. She sat alone at 6 months, walked at about 13 months, and began to say words at 18 months. From the onset her speech was hypernasal and quite unintelligible. The parents had always felt that this child was a little more awkward than her younger sibling, but this had become less noticeable as she grew older.

The regurgitation of food through the nares continued but in diminishing severity until the child was approximately 6 years old. Several physicians were consulted but no cause for the speech disturbance or for the regurgitation was established. She had received speech therapy for several years without noticeable improvement in her speech. At 7 years of age she was seen by a dentist who noted that the palate did not move normally and referred her to our Cleft Palate Clinic.

On physical examination she was shy, anxious, and constantly twirled or bit on a handkerchief. The palate was of normal configuration but no motion was noted on phonation. Neurological examination revealed no evidence of paralysis of any other muscles.

This child was obviously tense, anxious, and withdrawn. The mother felt that she had overprotected her in the early years because of the difficulties in feeding and speech but later expected her to conform to rather strict standards of behavior. Psychological testing revealed her to be of about average intelligence. The projective tests showed that she was denying hostile feelings directed toward the mother by passive resistance and displacement of this resentment to others.

A prosthesis was constructed to hold the palate in an elevated position, but the child would not tolerate the appliance. The nature of the child's physical and emotional problems was discussed with the parents and with continued counseling their attitudes toward her seemed to change. Despite the refusal to wear the prosthesis, the child's speech has improved somewhat and her emotional problems seem to have become less severe.

Case 2. S. G., an 11-year-old white girl, was born prematurely to a 39-year-old, gravida v, para v, Rh-positive mother following an uncomplicated vaginal delivery. Birth weight was 5 pounds. The pregnancy was complicated by several episodes of "colds and grippe" and the mother was "very, very sick" during the entire pregnancy. Shortly after birth the patient regurgitated milk through the nares but progressed well in other respects.

She sat alone at 8 months, walked at 16 months, and began to say words at about 20 months. In all of these performances she was slower than her siblings. From the onset speech was indistinct.

She was seen by several physicians because of difficulties in feeding and speech. At 3 years of age a tonsillectomy and an adenoidectomy were performed without change in her speech. At 9 years of age a dentist observed that the palate was "too long" and referred her to our Cleft Palate Clinic for evaluation.

The patient was the youngest of 5 children. There were no speech or neuromuscular disorders in any of the family members or relatives.

Physical examination was within normal limits except for the palate which was of normal configuration but which was observed

to have minimal to no motion on phonation. The speech was hypernasal and associated with nasal grimacing.

Psychological testing revealed an I.Q. range of 75 to 85. On projective testing it appeared that this child had problems centered around unsatisfied emotional needs, poor relations with the mother, feelings of insecurity, and rejection. The mother-child relationship seemed to lack the warmth and affection the child needed and desired. She was unable to express her anger with the mother for fear of rejection.

The patient's mother admitted that she had always considered her as the "ugly duckling." The child's development and academic performance were considerably slower than those of her siblings. She was an obvious source of irritation to the mother because of her speech difficulties and her constant desire to be the center of attention in the family group.

A prosthesis was constructed to elevate the palate, and speech therapy was carried out which resulted in considerable improvement. The nature of her emotional problems was discussed with the parents, but the period of observation has been too short to determine whether any beneficial changes have occurred.

Case 3. D. B., a 13-year-old white male, was born to a gravida ii, para i, 28-year-old female following an uncomplicated vaginal delivery and an uneventful pregnancy. The neonatal period was complicated only by regurgitation of feedings through the nares.

The patient sat alone at 6 months and walked at 15 months. He did not begin to say words until approximately 3 years of age, and speech was unintelligible from the onset.

Several physicians were consulted concerning the regurgitation and speech difficulties, but it was not until he was 6 years of age that a school physician observed that the palate did not move during phonation.

The parents had always felt that the patient had poor motor coordination; when he was 8 years old a neurologist was consulted who detected no obvious neuromuscular abnormalities. The patient underwent speech therapy for several years without improvement of his speech and was eventually referred to our Cleft Palate Clinic.

On physical examination he was somewhat awkward in his gross movements, but no specific neurological defects were noted. During phonation the palate moved minimally and appeared somewhat foreshortened. The speech was markedly hypernasal and barely intelligible.

Psychological testing revealed considerable range in intellectual capacities from mentally deficient to low average levels. He had been receiving psychiatric therapy for several years for emotional problems of a complex nature.

It was decided that continued speech therapy alone would not benefit his speech and that further psychiatric therapy without some effort to improve the speech would be of no avail. Therefore the decision was made to correct surgically the velopharyngeal insufficiency by suturing the palate to the posterior pharyngeal wall (the velopharyngeal flap operation). Postoperatively there was lessening of hypernasality and increased intelligibility of speech. The child's outlook improved; he requested that speech therapy be resumed. The relationship between the mother and child seemed to improve, although further observation will be needed to determine whether this improvement persists.

PATHOLOGY

The physiologic defect in "isolated palatal paralysis" is the failure of closure of the velopharyngeal space during phonation and deglutition.

During normal phonation velopharyngeal closure is effected by backward and upward movement of the palate, by constriction of the lateral pharyngeal walls, and, to a lesser extent, by forward motion of the posterior wall. The adenoids by virtue of their mass and location aid in making this closure. Palatal movement results from contraction of the levator palati, uvulae, palatoglossus, and palatopharyngeus muscles while the tensor palati keep the soft palate tense. The tensor palati are innervated by the mandibu-

lar nerve through the otic ganglion. All other palatal muscles are supplied by the pharyngeal plexus, formed by fibers of the glossopharyngeal and vagus nerves.

When viewed roentgenographically, the soft palate "knuckles" as it is pulled upward and backward by the contraction of the levators. The point of contact with the posterior pharyngeal wall is at about the midpoint of the dorsal surface of the soft palate. In deglutition the tongue participates in the velopharyngeal closure by pushing the palate upward and backward. This accessory action of the tongue explains the fact that regurgitation of feedings tends to lessen with age even though the speech defect persists.

Inadequate velopharyngeal closure in these cases resulted from limited or no movement of the soft palate. Although the soft palate seemed shorter than normal in 1 case, it appeared to be of normal length by cinefluorographic observation. Because of the lack of histologic and electromyographic studies, it is not known whether the pathologic involvement is primarily of the nervous innervation or of the muscles which control palatal movement. The slight palatal movement noted in 2 patients suggests that the involvement is not on an "all or none" basis.

Inadequate closure of the velopharyngeal space may also be produced by clefts of the palate, foreshortening (without paralysis), abnormal insertions of the palatal muscles, and occasionally by surgical removal of the adenoids. Palatal paralysis may result from damage to the peripheral nerves, from trauma, from infection as in poliomyelitis and diphtheria, or from involvement of the central nuclei by intracranial lesions. In the syndrome of nuclear agenesis described by Mobius, palatal paralysis, if present, is associated with paralysis of the facial muscles. The absence of signs of other neuromuscular weakness in "isolated palatal paralysis" makes the differential diagnosis from the above conditions less difficult.

ETIOLOGY

Not only is the site of the pathologic involvement unknown but there is no evidence at present to suggest the cause. Indeed, a single etiologic factor may not be operative in all cases. The disorder is apparently congenital as evidenced by the regurgitation through the nares early in the neonatal period.

The numbers of cases are too few to permit a significant analysis of the history of pregnancy and delivery. In one instance pregnancy was complicated by several episodes of "colds and grippe," but there were no apparent complications in the remaining cases. The delivery was described as uncomplicated in all cases.

The absence of other neuromuscular involvement makes it unlikely that the palatal paralysis is but one manifestation of a more widespread process. In 2 children there was a history of poor motor coordination early in life, but at the time of our examinations there was no residual evidence of this. Two of the children were of low average intelligence as demonstrated by psychological testing.

CINEFLUOROGRAPHIC OBSERVATIONS

Estimation of the degree of palatal movement, particularly in children, by direct observation is difficult. The technique of cinefluorography which utilizes rapid, motion picture roentgen exposures makes possible detailed study of palatal motion during phonation and deglutition. The clinical impression of palatal paralysis can thus be confirmed accurately.

Analysis of our cases revealed gradations in the degrees of movement observed from no motion to partial motion. In no case was the range of movement adequate to effect a contact of the palate with the pharyngeal wall.

In Case 1 there was complete absence of active palatal movement during phonation. The palate moved passively in certain sounds when pushed upward by the tongue. Regurgitation of a swallowed barium mixture was prevented by the tongue which pushed the palate upward and backward to seal off the velopharyngeal space.

In Case 2 there was a slight amount of "knuckling" indicative of some contraction of the levator muscles, but the velopharyngeal space was not closed. There was regurgitation of the swallowed barium mixture through the velopharyngeal space. With a prosthesis in place slightly more movement was noted, which suggests that some tension had been taken off the levator muscles by the appliance which held the palate elevated.

Case 3 exhibited the greatest amount of movement of the palate which, nevertheless, was inadequate to effect a junction with the posterior wall. The observations were made postoperatively, at which time the lateral and peripheral portions of the palate had been sutured to the pharyngeal wall. There was no regurgitation of the barium during swallowing.

TREATMENT

The basic aim of treatment is to effect a more adequate closure of the velopharyngeal space. In 1 case this was accomplished surgically by suturing of the soft palate to the posterior pharyngeal wall by the pharyngeal flap procedure. In 2 cases speech aid prostheses were constructed to elevate the dependent soft palate thereby narrowing the velopharyngeal space. This procedure seemed to improve the speech of 1 child, but the other would not tolerate the appliance.

All of the patients have received speech therapy, but we do not believe that the velopharyngeal insufficiency can be overcome by speech training per se.

Improvement in the quality of speech has been observed in all of the patients, but experience is too limited to predict which form of treatment will be preferable in a particular case.

In each of the cases, emotional problems of varying degrees of severity were present, and it is likely that the disturbed parent-child relationships were caused, or were intensified, by the concerns associated with the early feeding disturbances and with the speech disorders. It is reasonable to consider that these problems might have been lessened by earlier recognition and treatment of the physical defects.

SUMMARY

1. Three cases of paralysis of the palate unassociated with other neuromuscular involvement are presented, and the mechanism of production of the associated speech defect is discussed.

2. The importance of early recognition of this condition in prevention of the secondary emotional disturbances is stressed.

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Paralysis of the left diaphragm, left vocal cord, and aneurysm of the ductus arteriosus in a 7-week-old infant

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PARALYSIS of the diaphragm in the newborn infant is uncommon. The usual cause is birth injury. Although occurring alone, paralysis of the diaphragm is more commonly associated with brachial palsy. Schifrin[1] has reported a case of diaphragmatic paralysis, brachial palsy, and paralysis of the vocal cord in a 6-week-old infant due to birth injury. He considered this the first reported case of this association.

Malposition of the fetus in utero with extreme lateral flexion of the neck has been considered as a cause of phrenic nerve damage by Rupilius[2] and of recurrent laryngeal and superior laryngeal nerve damage by Chapple.[3]

The following is a case report of an infant who had paralysis of the left diaphragm and left vocal cord and at autopsy was found to have an aneurysm of the ductus arteriosus. To our knowledge this combination of abnormalities in a newborn infant has not been reported previously. The development of an aneurysm of the ductus in the newborn may be an additional cause of paralysis of the diaphragm and vocal cord.

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CASE REPORT

P. W., a 7-week-old boy, was admitted to The Children's Hospital of Winnipeg on Feb. 28, 1959. The complaints were difficult respirations, a weak cry, vomiting, and failure to thrive since he was 2 weeks of age. Birth had been by a cephalic presentation and was apparently uneventful. Nothing untoward had been noticed during the baby's stay in the newborn nursery.

Upon examination the infant appeared severely malnourished and had a gray color. The cry was weak and there was stridor on inspiration and expiration. The breathing was labored and gasping. There was a definite inspiratory tug with moderate indrawing of the chest. Entry of air on both sides was present but diminished. Repeated examinations did not reveal a cardiac murmur.

X-ray examination of the chest showed infiltrations of the right middle and lower lobes

consistent with pneumonia. The cardiovascular silhouette was not abnormal. Fluoroscopic examination showed marked paradoxical movement of the left diaphragm which indicated complete paralysis. Laryngoscopy showed absence of movement of the left vocal cord.

The infant was placed in a humidified environment with oxygen, and antibiotics were administered. After several days, the respirations seemed less labored than previously. Feedings were taken fairly well and vomiting did not occur. Twelve days after admission (March 12, 1959) fluoroscopic examination showed some return of movement of the left diaphragm. On March 15, 1959, 2 weeks after admission, the infant's condition began to deteriorate and on March 18 he suddenly stopped breathing following a feeding. Suctioning of the trachea produced a fairly large quantity of curds and mucus. Cardiac arrest occurred. The chest was opened and cardiac massage instituted. The heart began to beat and artificial respiration was maintained continuously. A tracheotomy was done and respiration was continued by machine (Bird residual breather). Treatment also included means of lowering the body temperature and intravenous fluids. The infant remained comatose, spontaneous respiration did not return, and despite all resuscitative measures death finally occurred on March 23, 1959.

PERTINENT FINDINGS AT AUTOPSY

The region of the ductus arteriosus was the site of a dark reddish-pink swelling. This swelling was oval in shape and measured 1.2 cm. in length by 0.9 cm. at its greatest diameter. The total length of the ductus was 1.5 cm. Both the aortic and pulmonary ends were completely closed and were represented by small dimples. The ductus was located in its normal anatomic position. The dilation of the ductus felt quite soft on palpation, and on incision, a brownish-red, friable blood clot was found completely filling the space. The wall of the enlarged ductus measured slightly less than 0.1 cm. in thickness. The thoracic portion of the vagus nerve was dissected and at the origin of the left recurrent laryngeal nerve it was seen to be very closely applied to the ductus, although it apparently was not stretched to any great degree. The relationship of the left phrenic nerve to the unusual ductus was disturbed in the dissection, but previous observation at operations for surgical closure of the patent ductus and subsequent dissections at autopsy disclosed that the phrenic nerve lay in very close relation to the region of the ductus (Fig. 1). There was no other cardiovascular abnormality. The lungs did not exhibit any gross evidence of pneumonia. The left leaf of the diaphragm had well-developed muscle fibers.

On microscopic examination the ductus contained a blood clot with minimal organization. Calcium was present in many areas throughout the periphery of the clot. In some areas a similar calciferous material was seen

Fig. 1. Photograph of autopsy specimen showing the left recurrent laryngeal nerve *(A)* coursing around and below the aneurysm of the ductus arteriosus. The left phrenic nerve *(B)* has been displaced lateral to the aneurysm in this photograph.

in the intima. There was focal intimal proliferation but generally the intima seemed thinned and compressed by the blood clot. Only at the aortic end of the ductus was there any cellular infiltration of the wall. This infiltration was associated with slight deposition of calcium along with pigment and hemorrhage.

DISCUSSION

In a review of 60 cases of spontaneous aneurysm of the ductus arteriosus by Cruickshank and Marquis[4] there were 51 cases in infants and 9 cases in adults. They reported a tenth case in an adult. Most of the aneurysms in infants were found accidentally at autopsy. Death, however, was due to rupture in 5 cases and to embolism in 3. Clinical signs and symptoms prior to death in the reported cases were not sufficient to direct attention to the aneurysm, but in 1 hoarseness had been noted.

The production of an aneurysm of the ductus arteriosus is related to changes in the wall of the ductus subsequent to its functional closure. The pulmonary end closes first and the pressure of blood from the aorta may stretch an already deteriorating wall to form the aneurysm. Intramural hemorrhage, trauma, and infection have also been advanced as causes of aneurysm of the ductus.

We have inferred that the presence of an aneurysm of the ductus in this case was the cause of paralysis of the diaphragm and left vocal cord since both the left recurrent laryngeal and the left phrenic nerves were applied closely to the aneurysm. There was no evidence of birth injury. The presentation was cephalic and there was no brachial palsy. The clinical features in this case did not resemble completely those in the infants described by Chapple[3] with a duosyndrome of the laryngeal nerve. In these cases damage to the recurrent and superior laryngeal nerves was considered due to extreme lateral flexion of the neck in utero with compression of the nerves between the cricoid and thyroid cartilages and the hyoid bone. Chapple states that these infants hold their heads turned away from the midline. One side of the face is weak or paralyzed from pressure by the uterine wall. The contralateral vocal cord is paralyzed producing dyspnea, inspiratory tug, and stridor. Damage to the superior laryngeal nerve results in difficult swallowing and regurgitation. Lateral flexion of the neck may also result in damage to the phrenic nerve or its roots. In our case there was no facial paralysis and the position of the head after birth did not suggest any abnormal intrauterine lateral flexion as suggested by Chapple as a prominent feature of his cases.

SUMMARY

A case has been presented of a 7-week-old infant who had paralysis of the left vocal cord and left diaphragm and who, at autopsy, had an aneurysm of the ductus arteriosus. The clinical picture obviously did not fit into the pattern of birth injury or intrauterine malposition, and it is suggested that the cause of the paralysis of the left vocal cord and left diaphragm was the aneurysm.

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TROPICAL PEDIATRICS

The pattern of early growth in Sukumaland, Tanganyika

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MWANZA, TANGANYIKA

IN RECENT years data have been published from many parts of the world, especially Africa, southeast Asia, the West Indies, and Central America, demonstrating that, by European and North American standards, growth is satisfactory only until about the age of 6 months.[1] It long has been held that an infant fed nothing but breast milk during the first 6 months of life grows and develops satisfactorily. Foman and May,[2] who recently have carried out a controlled study of infant feeding, found no evidence to the contrary. After this time, however, there is generally a definite slowdown in the gain in weight, as judged by the same standards, and this is attributed usually to difficulties which arise over mixed feeding and weaning and over intercurrent infections.

This problem has been studied particularly thoroughly by Welbourn[3] in the Baganda and other tribes living in the vicinity of Kampala, the chief town of Uganda. Much of our knowledge of kwashiorkor has been contributed by workers of the Kampala school,[4] and, in an area where the florid condition is so common, it is not surprising that Welbourn found that, in her experience in Child Welfare Clinics, about 50 per cent of all Baganda children of the toddler age have signs of prekwashiorkor. The staple food of the Baganda is steamed plantains (*matoke*), and mixed feeding normally is started at about 6 months of age by giving the child a lump of this or of sweet potato (*lumonde*) to chew, together with sips of tea. It is customary only after weaning to give any vegetable relish with the matoke, and the older children also get corn cobs and fruit when in season. Superimposed upon this background of retarded growth after the first 6 months, Welbourn has shown that infections such as gastrointestinal upsets, malaria, and especially respiratory infections, which are followed by a prolonged period of anorexia, often result in actual loss of weight, and sometimes lead eventually to overt kwashiorkor.

Mwanza is situated across Lake Victoria to the south of Kampala and is the provincial headquarters and chief town of Sukumaland in Tanganyika (Fig. 1). The most numerous inhabitants of this part are the Wasukuma (Fig. 2) and other related Bantu

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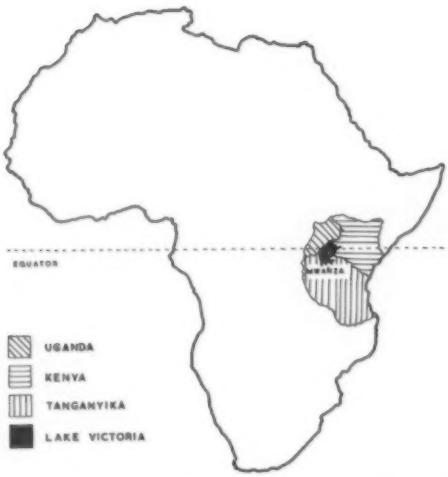

Fig. 1. Map showing location of Mwanza in Tanganyika.

Fig. 2. Typical Sukuma mother and young child.

peoples. It was thought that a study of the growth, feeding habits, and diseases of babies attending Child Welfare Clinics in and near Mwanza might afford an interesting comparison with the results from Kampala. Factors which might affect early growth, such as economic status, housing conditions, size of family, parental care, climate, and diseases of early childhood, are similar in the two areas. However, the common dietaries are quite different. Maize is the main staple in Mwanza, and maize gruel (*uji*) and, a little later, maize porridge (*ugali*) are the usual foods the baby receives as supplements. Tea is often given and a piece of boiled cassava (*muhogo*) placed in the hand of the child to chew. As in Kampala, only later are fruits and vegetables usually available to the child.

SOURCES AND NATURE OF DATA

The clinics. The Child Welfare Clinic, attached to the Government Hospital, Mwanza, has been in existence since 1950. It is supervised by a European Health Visitor, who is assisted by two trained African Health Nurses, one village midwife, and one *ayah* (African nursemaid). Child Welfare Clinics are held every Monday and Wednesday, and attendance averages about 120 each day. The mothers are encouraged to bring their children weekly during the first 3 months and, thereafter, once every 2 or 3 weeks. From the age of 15 months, they attend the Toddlers' Clinic held once a month. Most of the women attending the clinics live in the township of Mwanza or in its immediate vicinity.

All weighing is carried out by the *ayah*, who has been at the clinic since its inception. Babies up to 30 pounds are weighed on baby scales, and adult scales are used for toddlers. These scales are examined each year by a Weights and Measures official. Height is not recorded.

The Child Welfare Clinic, Misungwi, is now part of the Government Health Centre opened in 1958 in a village 30 miles south of Mwanza. The clinic, started in 1954, was held previously in the nearby village of Igokero. It is held twice a week and super-

Table I. Details of the records used

Situation of clinic	*No. of records*		*Babies born between these dates*	*Remarks*
	Male	*Female*		
Mwanza	87	99	March, 1953 to Jan., 1956	Mostly in 1955
Mwanza	49	50	Dec., 1956 to Dec., 1957	
Misungwi	48	52	Aug., 1954 to Nov., 1957	Mostly in 1956 to 1957

vised by an African Health Nurse. The Health Visitor from Mwanza comes once a month. It is organized similarly to the clinic in Mwanza but is supervised less closely.

The data. For the present investigation, only those records of children who had attended the clinic fairly regularly for at least 1 year were selected. Twins were not included, but there was no exclusion of those under a certain birth weight, thus making possible a comparison of these data with those of Welbourn. At the first visit, name, age, sex, tribe, and date of and weight at birth, if known, are recorded. As the first visit usually occurs when the baby is only a few weeks old, there is no difficulty in ascertaining the date of birth, even of those born at home. At each attendance, the baby is weighed unclothed, and notes as to feeding and to any illness are made by the Health Visitor or the Health Nurse. Birth weights were not used; in some cases, the baby had been born at home, and the birth weight was not known. If born in the hospital, the conditions under which the infant had been weighed in the ward differed from those in the clinic. Information on the feeding of the child was abstracted from each card selected for the study. Two items only were regarded as being of value: the time mixed feeding was started and the time breast feeding was ended.

Records of individual children were studied for the effect of feeding problems and intercurrent infections on growth. Details of the records used are given in Table I.

Tables were first constructed for each child of the weight and the age, in days, at each attendance. Weight-age curves were then drawn. These curves were used to find

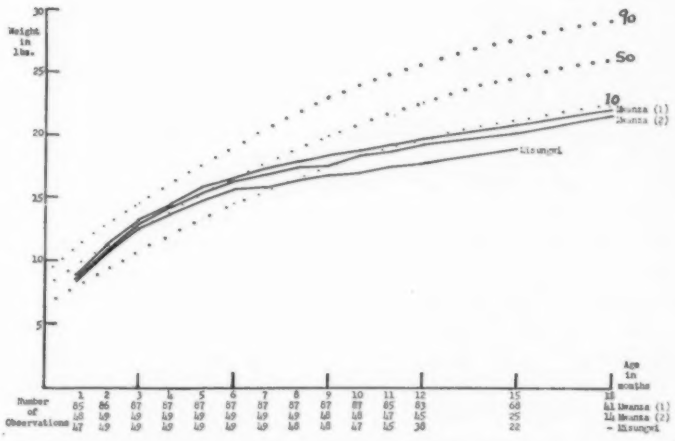

Fig. 3. Mean growth of male Sukuma infants. Dotted lines are percentiles for American boys.

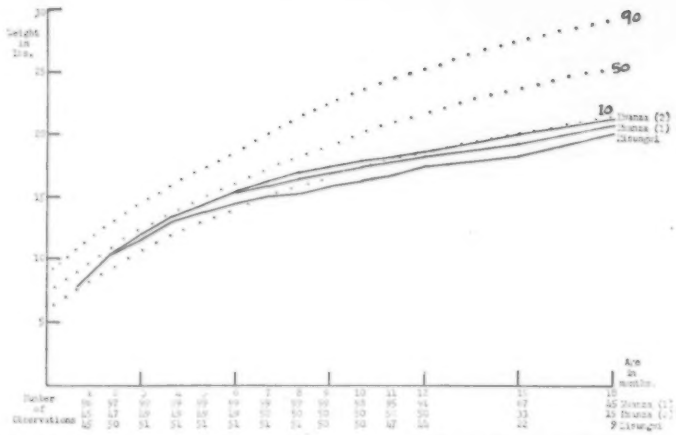

Fig. 4. Mean growth of female Sukuma infants. Dotted lines are percentiles for American girls.

the probable weights at regular intervals of 1 month during the first year and of 3 months thereafter. The means of the values obtained in this way were used to construct Figs. 3 and 4.

RESULTS

Growth. The weight-age curves in Figs. 3 and 4 represent the mean values for boys and girls during the two periods at Mwanza and the single period at Misungwi under study. These figures, for ease of comparison, have been drawn in the same way as those of Welbourn[5]; the percentile divisions of the standard figures taken from Stuart and Stevenson[6] in the fifth edition of the *Mitchell-Nelson Textbook of Pediatrics* have also been used.

Attendance at the clinic tended to fall off after about 1 year of age, and the numbers in each group after that time became rather small, as was the case at Kampala. The close similarity, for both sexes, of the curves for Mwanza and Kampala babies is striking. The curves tend to be smoother in the present data, and this is presumably because of the larger numbers used.

The curves for the two periods in Mwanza are practically identical. There is no reason to suppose that there would be any difference between these two periods, during both of which the clinic has been functioning and local conditions have not changed appreciably. They afford, however, a useful check on the comparability of this kind of data.

The growth of boys and girls at Misungwi fell well below that of those at Mwanza in both periods. An analysis of covariance (Table II) shows that the difference in weight at 1 year between the two groups attending the clinics at the same time (i.e., Mwanza, second group, and Misungwi) is significant beyond the 1 per cent level for both sexes ($F = 12.95$ for boys and $F = 9.07$ for girls). In the case of boys, however, the weights at 1 month of age were significantly higher for Mwanza infants, and this might have accounted for the differences at 1 year. On the other hand, there was no significant difference at 1 month for the girls. Thus, while the difference between the two groups is clear, the influence of birth weight is not.

Drillien[7] in Edinburgh has found that in the first 2 years of life, mean weights are closely related to mean birth weight and that boys show a greater weight increment than girls.

Table II. Analysis of variance between weights of infants in Mwanza and Misungwi in 1956 and 1957

Sources of variance	Sums of squares	Degrees of freedom	Estimate of variance	Variance ratio	Remarks
Males					
Weight at 1 month					
Within groups	98.36	93	1.06	19.26	Significant
Between groups	20.42	1	20.42		
Weight at 1 year					
Within groups	373.41	81	4.61	12.95	Significant
Between groups	59.70	1	59.70		
Females					
Weight at 1 month					
Within groups	137.64	88	1.56	2.59	Not significant
Between groups	4.05	1	4.05		
Weight at 1 year					
Within groups	520.66	92	5.66	9.07	Significant
Between groups	51.34	1	51.34		

Table III. Mean weights and weight increments for different weight groups at 1 month of male and female singletons

Age (months)	Weight at 1 month (ounces)	Weight (ounces)	Weight increment (ounces)	Number
Males				
6	Under 112	216.9	122.3	16
	112 to 127½	242.4	124.4	26
	128 to 143½	255.9	120.0	59
	144 and over	277.1	120.2	78
11	Under 112	273.9	179.3	16
	112 to 127½	285.2	168.2	23
	128 to 143½	294.5	158.6	58
	144 and over	314.4	157.5	74
Females				
6	Under 112	212.7	118.4	27
	112 to 127½	232.7	112.5	41
	128 to 143½	245.2	110.1	74
	144 and over	263.3	108.2	43
11	Under 112	263.6	169.3	26
	112 to 127½	271.6	151.4	39
	128 to 143½	284.3	149.2	70
	144 and over	306.1	151.0	42

In Table III all the present data have been pooled, and a comparison made of weights and weight increments of boys and girls divided into 4 groups on the basis of weight at the age of 1 month. The numbers were insufficient to go beyond a second period of 5 months at 11 months of age; up to this point, the same trends are evident, revealing no differences in the basic growth pattern in these widely differing environments.

Feeding practices. These were obtained from the records at the Mwanza clinic during the first period and are given in Table IV.

The most commonly used foods for the

Table IV. Data on certain feeding practices in Mwanza

Nature of information	*No. of records*	*Mean*	*Extremes*
Onset of mixed feeding	173	5½ months	3 and 10 months
Weaning (cessation of breast feeding)	68	15½ months	8 and 24 months

commencement of mixed feeding were maize gruel and tea, often in conjunction with orange juice and cod liver oil from the clinic. There is good reason to believe that in Mwanza, if not in Misungwi, the dietary instruction given to the mothers (Table V) is followed, at least in principle, by many.

Individual records. An answer was sought to 2 questions by a consideration of individual records. The first was the role which various infections may play in temporarily or permanently retarding growth. Fig. 5 illustrates how the growth of a child who receives a good diet is less affected than that of one who is poorly fed. Sudden loss of weight is rapidly regained when feeding is satisfactory, and there is no interference with the rate of growth (Case No. 47). A series of illnesses, such as malaria, bronchitis, and gastrointestinal upsets, together with a period of separation from the mother, due to her contracting pulmonary tuberculosis, resulted in the complete cessation of gain in weight in one (Case No. 57) for about 250 days. When conditions improved, weight was put on at the former rate. Sickle cell anemia was responsible for the very poor growth and ultimate death at the age of 2 years and 1 month of another (Case No. 116). Finally, one (Case No. 171) showed how continual illness may have almost no effect on growth when the diet is very good.

The second question was: What kind of records do children show who have the highest weights at the end of 12 months? A weight of 24 pounds and over was arbitrarily chosen, and 8 Mwanza babies, but no Misungwi infants, qualified. Table VI gives details of these, and Figs. 6 and 7 show their growth graphically.

All of these babies were heavier than the average by the age of 1 month, but they did not have high birth weights necessarily. In one instance (Case No. 97), it was well below the average at 5 pounds, 15½ ounces.[8] When the growth curves of these heavy babies are compared with the American standards, it is evident that it is possible for African babies, under the most favorable circumstances, to attain growth equal to, or even better than, the average in the West during the first year of life. Genetic factors, as reflected by heights of parents, have been shown to play a part equal in importance to that of environmental factors,[7] and the lower mean stature of the Wasukuma (see footnote to Table VII) must be taken into account when growth is considered.

Six of these 8 babies had almost no illnesses during this period. In one (Case No. 121), short attacks of malaria and bron-

Table V

Age (months)	*Diet*
1	Orange juice and cod liver oil
4 to 5	Morning feed of *uji* with a little sugar and milk added
5 to 6	Midday soup made of gravy from meat, beans, or boiled fish
6	Vegetables introduced into midday meal (usually amaranths and tomatoes and occasionally cabbage or carrots)
7	Evening meal of *uji*, beans cooked with peanut oil, or a boiled egg
9	Fish added to midday meal; rice added at midday or evening
	Fruit—pawpaw, bananas, oranges, mangoes, in season
	Given nonfat dry milk from clinic if growth appears unsatisfactory (introduced only in April, 1958, so does not appear in present study)
12 to 14	Weaning advocated
15	Introduction of meat

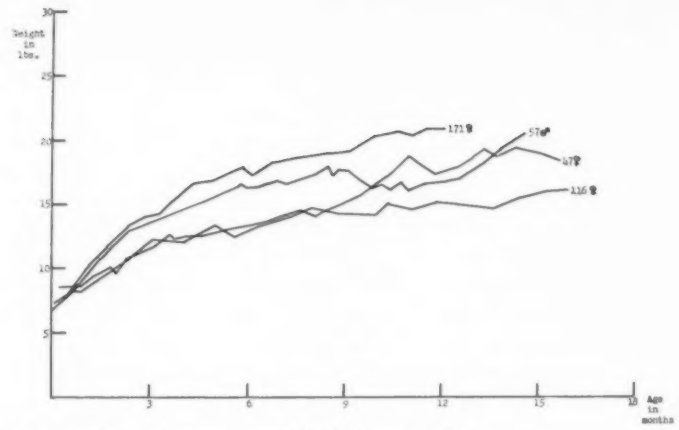

Fig. 5. Individual growth records of Sukuma infants.

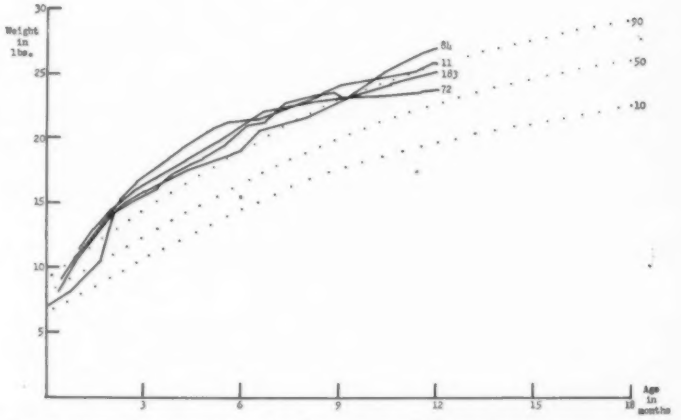

Fig. 6. Growth of exceptional male Sukuma infants. Dotted lines are percentiles for American boys.

chitis had only a temporary effect on growth, and in another (Case No. 1), repeated febrile illnesses throughout failed materially to affect growth. One infant (Case No. 97) was the fifth child, and all the other children were alive. Despite this, and the low birth weight of 5 pounds, 15½ ounces, the high weight of 24 pounds, 6 ounces was achieved at 12 months.

DISCUSSION

In the preceding pages, certain evidence has been presented in support of the contention that the pattern of early growth in Sukumaland follows that reported commonly from many other parts of the tropics.[1] Special comparison has been made with the data from Kampala because of the suitable nature of the latter and also because of the

Table VI. Certain details of 8 exceptional infants

Record No.	*Sex*	*Clinic*	*Weight*						*Illnesses*
			At birth (pounds, ounces)		*At 1 month (pounds, ounces)*		*At 12 months (pounds, ounces)*		
1	F	Mwanza first period	Not known		8	8	24	2	Repeated febrile illnesses throughout
121	F	Mwanza first period	8	4	11	11	26	1	Occasional malaria and bronchitis with only temporary effect
11	M	Mwanza first period	8	6	10	8	25	12	Little illness
72	M	Mwanza first period	7	3	8	12	24	0	Little illness
183	M	Mwanza first period	Not known		11	7	24	12	Little illness
53	F	Mwanza second period	8	2½	10	0	26	12	Little illness
97	F	Mwanza second period	5	15½	9	2	24	6	Little illness
84	M	Mwanza second period	Not known		11	9	26	14	Little illness

Table VII. A comparison of environmental factors

	Kampala	*Mwanza*	*Misungwi*
Growth	Mean below 10 percentile of American standard by 12 months	As Kampala	Lower still
Feeding practices	Mixed feeding 4 to 5 months Weaning 14 to 15 months	As Kampala	Not investigated, but verbal evidence indicates later for both
Diet	Mainly plantain	Mainly maize	As Mwanza
Social condition	Semiurban, semieducated (main group of study)	As Kampala	Rural, noneducated
Infectious diseases	Respiratory, gastrointestinal, malaria (in order of importance for this study)	As Kampala	As Kampala
Genetic			
(A) Race		All Bantumorphs	
(B) Parents' height		No striking differences*	
Influence of clinic	Probably considerable	As Kampala	Probably much less
Clinical signs	Prekwashiorkor in 50%, frank kwashiorkor common in hospitals of area	Very rarely prekwashiorkor or kwashiorkor in hospital	Some prekwashiorkor but more marasmus seen in clinic

*Mean for Wasukuma males—168.9 cm. (From our data).
Mean for Wasukuma—168.0 cm. (From Oschinsky[23]).
Mean for Baganda—165.96 cm. (From Oschinsky[23]).

proximity of the two places and the similarity of many factors which might play a part in affecting growth. Further, in view of the important role usually attributed to nutritional factors, the marked difference in diet between the two peoples made such a study of special interest. These and other points of comparison and contrast are shown in Table VII.

Possible role of dietary differences. The two salient points from Table VII which require explanation are the similarly poor growth in Kampala and Mwanza, despite the apparently better diet and much lower incidence of overt malnutrition in the latter place, and the still poorer growth in the rural Wasukuma of Misungwi.

The inadequacy of plantain as a staple, with its very high water (70 per cent) and low protein (1 per cent) content is obvious. At first glance, maize might seem to be a much better staple, with about 10 per cent protein, but its weakness would appear to lie in the composition of amino acid of its proteins. Supplementation of diets of maize fed to patients recovering from kwashiorkor in Guatemala[9] and to normal male subjects in South Africa[10] has shown that maize protein is deficient in tryptophan, lysine, and isoleucine. In the treatment of kwashiorkor, supplementation of maize with these three amino acids gave as strongly positive nitrogen balances as with milk. In the South African study, replacement of half the maize protein by casein or milk resulted in retention of nitrogen by subjects who previously had a small positive balance.

In the Guatemalan cases of kwashiorkor, however, nitrogen balances as strongly positive as those obtained with milk did not result until maize was supplemented with all three deficient amino acids. From a consideration of the amino acid composition of human milk, it would appear that a diet of maize and milk would still be deficient in lysine, isoleucine, and tryptophan. Furthermore, all essential amino acids must be supplied simultaneously,[11] and there will be times when the African infant receives only one source of protein at a time. It would seem then, that, under the conditions of infant feeding in the tropics, there may be little to choose between steamed plantain (*matoke*) and maize gruel (*uji*) as a supplementary food to breast milk.

The high incidence of prekwashiorkor signs in the clinics and of kwashiorkor cases in the hospitals in Kampala, would seem to

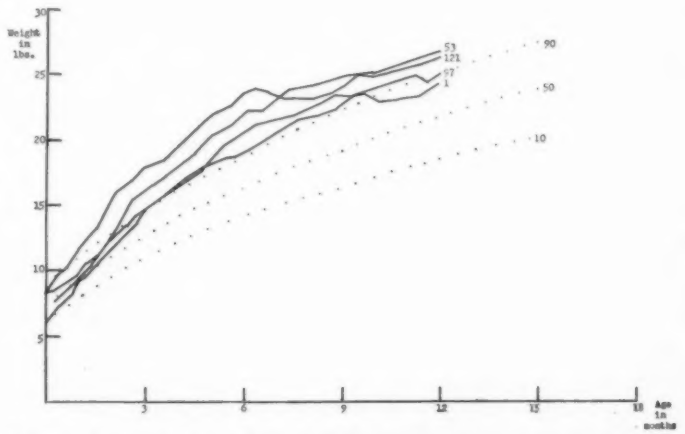

Fig. 7. Growth of exceptional female Sukuma infants. Dotted lines are percentiles for American girls.

be related, at least in part, to the low protein/calorie ratio of infants' diets, as has been observed repeatedly by workers in that area. It may be that a lower intake of carbohydrate from the cereal diet in Mwanza might account for the rarity of kwashiorkor signs in the infants in the clinic and hospital.

In rural Sukumaland, the poorer growth and the frequent occurrence of marasmus would seem to be due to a combination of both caloric and protein undernutrition. Many of these children appear "half starved," and while the diet is basically the same as that in Mwanza, the difference may possibly be explained by a superimposed caloric deficiency resulting from the later introduction of mixed feeding, the undue prolongation of breast feeding, and the lesser influence of clinic teaching.

For completeness, reference should be made to a more recent paper of Welbourn[12] in which a comparison was made of the growth of a very small number of Luo infants with the Baganda data. It was concluded that although the Luo were not as clean and less well cared for, they grew better. Their diet, after mixed feeding was instituted, resembled that of Mwanza infants. It seems unjustifiable to draw this unexpected conclusion from the very small number of Luo infants studied. It should be noted that, of all the tribes studied by Oschinsky,[13] the Luo exceeded the Baganda in height by the greatest amount. This might well account for the infants being larger.

Importance of other illnesses. The interplay of nutrition and infections has been illustrated from the Mwanza data and confirms the conclusion of Welbourn that infections have less effect on the growth of the well-nourished infant than on one having a poor diet. Here, too, respiratory disease probably has greater importance than malaria in retarding growth. In the Gambia, McGregor and colleagues[14] concluded that acute clinical malaria caused a temporary retardation of growth during the first 18 months of life, but that by the third year, the unprotected infants weighed as much as those protected by an antimalarial drug, although enlarged livers and spleens must have contributed disproportionately to their weight. The variable effects of malaria on the growth of infants in Nigeria found by Bruce-Chwatt[15] may have been due to differences in nutrition.

Welbourn postulates, as others have done, that infantile malnutrition leaves its mark on the individual throughout life, and there is evidence that the aging process is accelerated in malnourished tissues and organisms. It is clear from a new concept of aging, which Jones[16] has recently propounded, that not only nutritional factors, but all disease processes need to be taken into account in determining the physiologic age of individuals and populations. In outline, he states that the tendency toward further disease experience is at a rate determined by accumulated disease experience of the past. Among this disease experience, that occurring in childhood may be the most important in determining the ability of adult populations to survive.

SUMMARY

Child Welfare Clinics in Mwanza and Misungwi provided records of the growth and feeding practices of 385 African children during the first 18 months of life.

The Mwanza data are almost identical to those from Kampala,[3] but those from rural Misungwi indicate inferior growth.

The different effect of intercurrent infections in the well and the ill nourished is illustrated, and a special study of a few infants shows how exceptional growth may be attained under favorable circumstances.

Finally, an attempt is made to explain the differences in growth observed in the three places mentioned above by a consideration of such varying factors as diet, feeding habits, social conditions, infectious diseases, genetic characteristics, and influence of the clinics.

I am much indebted to Miss W. R. Urquhart, Health Visitor in charge of the clinics where the studies were conducted, for her enthusiastic help and encouragement. My thanks are once again due to Dr. R. G. P. Heard, Medical Officer in

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MEDICAL PROGRESS

Current concepts of potassium metabolism

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IT IS, I am sure, no accident that, on the one hand, many outstanding contributions to electrolyte metabolism have been made by practicing pediatricians, and, on the other hand, students of electrolyte metabolism have found themselves drawn to the study of the neonate and even the fetus.[1] Babies contain relatively more fluid than grown-ups, and their daily turnover of fluid is greater still, representing about half the total body content.[2] In diseases of infants, the problems of fluid balance are inescapable, and by 1945 the techniques for maintaining sodium and water balance were generally effective. The stage was then set for the critical observation of Darrow[3] that infants who survived the acute stages of gastroenteritis, largely by dint of salt and water replacement, were left in a state of potassium depletion. Experience since then has multiplied the syndromes in which depletion of potassium can be recognized and has also shown that it is not a biochemical curiosity, but a cause of symptoms, of structural lesions, and even of death. The pediatric contribution to these advances has been so outstanding as to enforce a salutary modesty on anyone like myself whose clinical experience is practically limited to the *soi-disant* mature adult. I can only hope that some uncovenanted mercy of perspective may be bestowed by a somewhat detached view of the clinical part of the problem.

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AMOUNT AND DISTRIBUTION OF POTASSIUM

The total amount of potassium (K) in the human body has been estimated by analysis of cadavers, by dilution of the isotope, K^{42}, and by measurement of the whole-body radiation emitted by the naturally occurring radioisotope K^{40}.

The results of analysis of cadavers are few in number, but later estimates[4, 5] are in general agreement with the estimate of Shohl[6] calculated from the older literature. Shohl's figure is 150 Gm. of potassium in an adult who weighs 70 kilograms, or 54.8 mEq. per kilogram. Rundo and Sagild[7] estimated total body potassium from the radiation emitted by the K^{40} of the body; in 6 young men, their mean finding was 0.215 per cent, i.e., 55 mEq. per kilogram. In the same subjects, the mean finding for "exchangeable K," based on dilution of K^{42}, was 0.19 per cent, i.e., only 48.7 mEq. per kilogram. This figure falls in the usual range of estimates based on K^{42}; the estimates of total body potassium by analysis and by K^{40} are few in number, but they agree with one another and seem sufficient to justify the conclusion of Edelman and Leibman[8] that about 10 per cent of the total body potassium may not be ex-

changeable readily. A small part of the slowly exchangeable potassium of the body can be accounted for by the red cells, brain, and bone. The site of the rest is not known, but it may represent no more than the summation of various sites in the body whose supply of blood is scanty. Although K^{42} injected intravenously leaves the plasma rapidly by exchanging with K^{39} already in the tissues,[9] a depot of K^{42} established in tissue of the forearm is still appreciable 24 hours later.[10]

For obvious reasons the great majority of the available estimates of "body-potassium" have been made by the K^{42} technique. Edelman and Leibman[8] have collected results obtained in this way. In 73 males aged 18 to 33 years the mean result was 48.9 mEq. per kilogram; in 72 females aged 16 to 33 years the mean result was 37.3 mEq. per kilogram. The lower potassium content of women can be partly accounted for by their smaller lean body mass; when the potassium content is expressed as mEq. per liter of body water, the figure in men is 80.4 and in women 75.3. This residual discrepancy is probably due to the smaller proportion of muscle tissue in women. Corsa and colleagues[11] have determined exchangeable potassium in 16 "hospital-normal" infants and children up to 16 years of age. In this small group, they found a mean of 40 mEq. per kilogram, which did not differ from their finding in young adults. Their figure is, however, lower than the collected figures for young adults, and this would be reasonable in view of the well-known high proportion of extracellular fluid in the infant which would be expected to "dilute" the cell mass rich in potassium. It is relevant to mention here that in muscle obtained by biopsy from infants, Frank and associates[12] found a mean potassium content of 33.5 mEq. per 100 Gm. of fat-free solids, a value which is lower than the corresponding figure of 44.7 mEq. found in adults (Litchfield and Gaddie[13]). Forbes[14] indicates a gradual increase in potassium (as milliequivalents per kilogram) from intrauterine to adult life.

Potassium is predominantly an intracellular ion, and the amount of potassium in the various tissues depends on their bulk and their cellularity. For example, in a man who weighs 70 kilograms and has 3,800 mEq. of potassium, the muscles weigh 30 kilograms and contain 2,730 mEq. of potassium, whereas the skin and subcutaneous tissue, which weigh 18 kilograms, contain only 360 mEq. of potassium.[15] The partition of potassium among the various organs has in fact less physiologic and pathologic relevance than the distribution of potassium among the main divisions of body fluid, often described as "compartments." Looked at in this way, the great bulk of body potassium is in intracellular fluid, but there are significant amounts also in plasma and extracellular fluid, in bone, cartilage, and dense connective tissue, and in "transcellular" fluids such as the contents of the alimentary tract and the cerebrospinal fluid. Table I shows the relative amount and the concentration of potassium in these categories of body fluid. This type of analysis brings out rather

Table I. Potassium in the main divisions of body fluid from the data of Edelman and Leibman[8]

Type of fluid	*Per cent of total body water*	*Per cent of total potassium body*	*Concentration of potassium (mEq./L.)*
Total body water	100	100	90.0
Water in plasma	7.5	0.4	4.4
Extracellular fluid	20.0	1.0	4.2
Water in connective tissue and cartilage	7.5	0.4	4.4
Water in bone	7.5	7.6	91.0
Intracellular water	55.0	89.6	146.0
Transcellular water	2.5	1.0	33.0

clearly the high concentration and amount of potassium which are found inside the cells. Another point of interest is the high concentration, relative to other extracellular fluid, of the potassium in "transcellular" fluid; since this mainly represents the contents of the alimentary tract, it indicates the considerable importance of gastrointestinal disease in producing clinical depletion of potassium. It is also worth noting that the concentration of potassium of intracellular fluid, based on space measurements, i.e., 146 mEq. per liter, is in fair agreement with the mean result calculated from analysis of human muscle (164 mEq. per liter).[13] This agreement is perhaps to be expected in view of the high proportion (about 70 per cent) of total potassium which is found in muscle tissue, but it supports the validity of the two rather different assessments. There may, of course, in tissues other than muscle, be considerable local differences in the concentration of potassium, notably in secretory tissue, but it seems that the mean concentration of potassium of intracellular fluid in other tissues is not grossly different from that in muscle.

The intracellular location of potassium and the converse extracellular location of sodium present a challenge to investigators who have not as yet agreed on a solution. The idea of a cell wall which is impermeable to both these cations can indeed be firmly rejected in view of the many demonstrations, most notably with isotopes, that no such barrier exists; there is, however, no decisive evidence to choose between the two main theories of a "sodium-pump" and of intracellular binding of potassium. What is clear and common to both theories is that the maintenance of the electrolyte gradient across the cell wall depends on the supply of metabolic energy and is indeed a significant charge on the energy-producing reactions within the cell, whether these are deployed directly in "pumping" ions or indirectly in maintaining cellular organization. When tissue is damaged, there is a loss of potassium from the cells, both in association with the loss of nitrogen of protein breakdown and also in some cases independently of the loss of nitrogen. This second happening is often summarized as "loss of K in excess of N" and is demonstrable for the body as a whole in the course of balance studies. Apart from cellular breakdown the balance of potassium between cells and extracellular fluid is influenced by a number of other factors, some of which have clinical relevance and will be discussed later.

REGULATION OF BODY POTASSIUM

As with other electrolytes, potassium is not created or destroyed in the body, so the amount in the body depends on a balance between intake and output, which remains nearly constant in healthy adult life, with only minor fluctuations from day to day. In the growing organism, the situation is somewhat different, since growth of tissue involves the accretion of cellular potassium so that the over-all balance must be positive. The rapid entry of potassium into tissue in infancy may enable doses of potassium to be tolerated by infants, when comparable doses of potassium in adults would lead to toxic effects; there is also evidence that the infant can withstand concentrations of potassium in the serum which would be toxic in adults. McCance and Widdowson[16] have found a mean-concentration of potassium in serum of 10.2 mEq. per liter in 3 fetuses and 8.0 mEq. per liter in 5 newborn infants. Further investigation of neonatal serum composition is indicated, but in the meantime it may be noted that exchange transfusion may be carried out safely, although it may entail concentrations of serum potassium which would be considered toxic in the adult.[17]

The normal intake of potassium is dietary, and all foods of animal or vegetable origin contain useful amounts of potassium. The intake of potassium in a normal adult diet ranges from 50 to 150 mEq. per day; since the man is in potassium balance, this amount will also be excreted, mainly in the urine, but to a small extent in the feces and sweat. In a man who weighs 70 kilograms, has 3,150 mEq. of potassium, and consumes 100

mEq. per day, the "turnover ratio" will be 1/31.5. The situation in the growing child is different in two respects. First of all, as already mentioned, not all the dietary potassium will be excreted; some will be retained for growth of tissue, and an infant increasing in weight from a birth weight of 3.5 kilograms to 7.0 kilograms will have to find 140 mEq. of potassium from a diet which initially contains only 6 mEq. per day, and rises only to 12 mEq. per day. Second, and perhaps partly because of this, the apparent turnover, as judged from dietary intake and body content, will be substantially larger than in the adult, of the order of 6/140, i.e., 1/23. These figures assume a birth weight of 3.5 kilograms, and an intake of human milk increasing from 0.5 L. per day to 1.0 L. per day at 20 weeks. Because of retention during this time, the excretion will be only 1,120 mEq. out of a total intake of 1,260 mEq. Even so, the daily mean turnover, based on excretion rather than intake, will still be 8/210, i.e., 1/26, which is still a little higher than the figure in adults. In infants fed on cow's milk, the turnover will be higher still, for even half-strength cow's milk contains about twice as much potassium as does human milk. To set these calculations in perspective, however, it should be pointed out how much less striking they are than the very high turnover of fluid which is shown so clearly for the infant in the well-known diagram of Gamble.[2] The infant of course needs potassium for growth and is perhaps helped in getting it by a somewhat high intake in relation to his body content, but a transient deprivation of potassium will only be catastrophic if aggravated by abnormal losses of potassium from the body.

The dietary intake of potassium is, of course, subject to random variation; the responsibility of maintaining body potassium in face of this rests upon the kidneys, whose behavior is subject to endocrine regulation. There is now a good deal of evidence, summarized by Black and Emery[18] that very little if any of the potassium filtered in the glomeruli appears in the final urine; the urinary potassium represents potassium which has entered the tubule fluid in exchange for sodium which is being reabsorbed. This proposed mechanism of potassium excretion minimizes the importance of hemodynamics in potassium excretion and brings it in more direct relation with cellular potassium; it also relates it to acidification of the urine, for hydrogen ions are supplied to the urine by a similar exchange process, and under certain conditions a reciprocity between the excretion of potassium and hydrogen is demonstrable.[19]

In a normal person the giving of potassium salts leads to a corresponding increase in the renal excretion of potassium, and, conversely, a diet low in potassium leads to a progressive decrease in the potassium content of the urine. The conservation of potassium is, however, less prompt and absolute than that of sodium under corresponding conditions.[20] Conservation of potassium can occur without any fall in the plasma level of potassium or in the glomerular filtration rate; conversely, excretion of potassium can be maintained in spite of induced reduction in glomerular filtration. The relative importance of low intracellular concentration of potassium and of diminished production of aldosterone in lowering output of potassium on a low potassium diet has not yet been established. Aldosterone is the most potent "salt-active" hormone of the adrenal gland, and its action in respect of potassium is to increase excretion of potassium, without any increase in the level in plasma. The glucocorticoids can also increase excretion of potassium, but their effect is smaller, and there is some evidence that it may be extrarenal rather than renal.[21]

The normal amount, distribution, and regulation of body potassium have been outlined since the causes and severity of change in body potassium can be assessed only in relation to the normal metabolism of potassium. Similarly, in order to understand the effects of clinical depletion and excess of potassium, it is necessary to know something of the physiologic significance of potassium, even though present knowledge in this field is still far from complete. It is important to

distinguish between the small, but important, moiety of potassium which is extracellular and the larger mass of potassium within the cells.

SIGNIFICANCE OF EXTRACELLULAR POTASSIUM

The concentration of potassium in the extracellular fluids is assessed in practice by estimation of the potassium concentration in plasma or serum (plasma potassium). In normal people, 98 per cent of values lie between 3.5 and 5.6 mEq. per liter and 80 per cent of values between 3.9 and 5.0 mEq. per liter.[22] Because of the much higher concentration of potassium in erythrocytes, accurate results for plasma potassium are obtained only when hemolysis is avoided and red cells are promptly separated from the plasma. When the amount of potassium in the body changes, plasma potassium usually, but not necessarily, changes in the same direction; the exceptions are numerous enough to make plasma potassium a rather unreliable guide to the state of potassium balance. On the other hand, they are instructive when we are concerned with the separate significance of plasma potassium. Plasma potassium can be *decreased,* independently of over-all depletion of potassium, when anabolism of protein or deposition of glycogen in cells are proceeding actively, in alkalosis, whether metabolic or respiratory, and during the attack in familial periodic paralysis. Plasma potassium can be *increased,* again independently of over-all potassium excess, when breakdown of tissue is rapid and in states of acidosis.

Our knowledge of hypokalemia is based on observation of states in which it occurs independently of depletion of potassium, on experiments with organs perfused with media of low potassium, and to some extent on the effect of treating patients depleted of potassium with infusions of potassium salts sufficient to raise the plasma potassium but not sufficient to correct intracellular depletion of potassium to any great extent.[23] The most definite effects are apparent in the action of muscle of different types. There is weakness of striated muscle, with diminished reflexes, and this may extend to the muscles of respiration, including the diaphragm. The smooth muscle may be affected, giving rise to paralytic ileus in the intestine, and to hypotension in the blood vessels. The cardiac action is weakened with arrhythmia and tachycardia and E.C.G. changes which include prolonged Q-T interval, T-wave inversion, and the appearance of U-waves. These effects on muscle may have a common basis in a diminished inflow of potassium into cells, following the sudden outflow of potassium which accompanies excitation. Other effects of hypokalemia are less striking and definite; they include mental confusion, lethargy, and tachypnea, all of which also have many other causes, in contrast to the pathognomonic effects on muscle.

The effects of hyperkalemia are less familiar, but equally striking, and in extremes even more dangerous. Muscle weakness also occurs, but presumably on a different basis, which may be a low membrane potential, which is proportional to the logarithm of the ratio of intracellular to extracellular potassium. The nervous system may be involved, with paresthesia, and rarely an ascending paralysis of central rather than peripheral origin. The cardiac effects include arrhythmia, peaked T-waves, and ultimately arrest at a level of plasma potassium of the order of 10 mEq. per liter.

In summary, the significance of extracellular potassium lies in its neuromuscular effects, in the relative ease with which it can be measured, and in the catastrophe latent in uncontrolled hyperkalemia.

SIGNIFICANCE OF INTRACELLULAR POTASSIUM

Although potassium is abundant within cells, it cannot be directly measured there, and clinical observations are confused by the changes in extracellular potassium which generally accompany changes in intracellular potassium. It is true that measurement of erythrocyte potassium is temptingly easy, but it is doubtful if the results are of much value in relation to the general mass of in-

tracellular potassium; red cell potassium has a very much slower rate of exchange than tissue potassium, and many of the alterations which have been described in it are really changes in intracellular water, of which potassium is the predominant cation. The concentration of potassium in intracellular fluid is similar to that of sodium in extracellular fluid, and it is therefore plausible to ascribe an *osmotic* function to intracellular potassium. It has been shown that depletion of potassium is attended by a fall in volume of intracellular fluid, and, conversely, that primary water depletion, which imposes a lower volume of intracellular fluid, leads to loss of potassium from the body. It has also been shown, both by isotope[24] and by balance observations[25] that in constructing a valid osmotic balance one must take potassium into account on the same basis as sodium. It can be inferred that the greater part of intracellular potassium is in an osmotically active form, but the presence of small and possibly variable amounts of osmotically inactive or "bound" potassium cannot be excluded by this type of evidence. In the same way, on purely quantitative grounds, potassium must have great importance as an intracellular cation. In states of depletion of potassium, there is evidence of an intracellular acidosis,[26] and also of a partial replacement of the lost potassium by other cations such as sodium and organic bases, notably lysine. Apart from the rather obvious significance of intracellular potassium in relation to osmolarity and electroneutrality, there is increasing evidence that concentration of potassium is one of the critical components of the intracellular milieu for enzyme action associated with production of energy, storage, and cellular growth. Among the enzymes for which concentration of potassium has been found to be important are phosphotransacetylase, acetyl-CoA synthetase, pantothenate synthetase, pyruvate phosphokinase, and myosin ATPase.[27] The effect of potassium on enzyme systems is commonly antagonized by sodium, and it may be that some of the general effects of intracellular depletion of potassium are in fact mediated by the increased entry of sodium into the cells, which is imposed by the demands of osmolarity and electroneutrality in depletion.[28] It has also been shown in the whole animal, as opposed to isolated enzyme systems, that such depletion leads to impaired use of carbohydrate and protein synthesis. That severe depletion represents a biochemical insult of some flagrancy is now established, and there is also good morphologic evidence that it can lead to necrosis of the tissue in the heart, kidneys, and muscles. The part which it may play in causing symptoms is much less definite, especially when allowance is made for the separate effects of changes in extracellular concentration and for the general "ill-being" of the primary disease causing depletion. I believe that a clue to the solution of the strictly clinical dilemma may lie in the small number of studies on experimental depletion of potassium which have been carried out in man.

EXPERIMENTAL POTASSIUM DEPLETION IN MAN

A number of studies[20, 29, 30-33] have been made in which dietary restriction of potassium has induced a loss of potassium from the body of up to 400 mEq., or about a tenth of the total potassium in the body. The subjects in these studies have shown no definite symptoms and have been able to continue their usual work. A greater depletion of potassium cannot easily be produced by dietary restriction alone, because loss of potassium in the urine becomes very small in a few days. However, Fourman[34] used an exchange resin in the ammonium cycle to induce depletion of 670 mEq. and 840 mEq. in 2 normal subjects, a degree of depletion twice as great as in other studies. His subjects were weak and apathetic, sensitive to cold, confused, anorexic, and thirsty; these are all symptoms which have been observed in clinical states of depletion of potassium, but their occurrence in otherwise healthy subjects is perhaps more convincing evidence that they are in fact related to such depletion. There is, of course, no doubt that the

severe degrees of depletion, which can be induced in animals, lead to ill-being, morphologic changes, and ultimately death. Taking the results of these different studies together, it seems to me useful in patients to distinguish between moderate depletion, of the order of 10 per cent of body potassium, which is fairly common and usually causes no particular symptoms, and severe depletion, with loss of 15 per cent or more of the body potassium, which is much less common, but causes notable symptoms and constitutes a real threat to life. It should be recognized, however, that even moderate depletion, which is generally symptomless, may lead to muscular weakness, when it happens to be associated with hypokalemia. A good example of this can be found in patients with diabetic ketosis, who have a moderate degree of depletion, amounting in one series to an average of 8.2 per cent of total body potassium.[35] While they have an acidosis, their serum potassium is normal or even increased, and they have no symptoms of depletion; when the acidosis is corrected, the serum potassium falls to a variable degree, which may perhaps be related to the phase of respiratory alkalosis which can sometimes follow enthusiastic "correction" of diabetic ketosis.[36] Even so, only a small minority of patients show any muscular weakness, even at this stage, and it is in these that the lower levels of serum potassium are to be found. Some emphasis on these two distinctions (between the effects of hypokalemia and of over-all depletion and between moderate and severe depletion) may make the symptoms of depletion more clear than they sometimes have been in the past.

Although a distinction between moderate and severe depletion is perhaps the chief clinical fruit of these experimental studies, some of the individual findings are also of interest. Most subjects have retained sodium as they lost potassium, and some have even become edematous. Thirst has been observed in those with severe depletion, but not in those with moderate depletion; tetany has been seen in a few subjects. For most of the strictly biochemical findings, the reader is referred to the original reports, but in view of the clinical interest in so-called "hypokalemic alkalosis," this topic may now be discussed.

ALKALOSIS ASSOCIATED WITH DEPLETION

Potassium metabolism and acid-base balance are interrelated in a number of ways, including these.

1. A primary acidosis increases the passage of potassium from cells into extracellular fluid, and this may promote excretion of potassium as well as raised levels of plasma potassium; primary alkalosis has a converse effect at this level.

2. On the other hand, in the renal tubule there is an exchange of both potassium and hydrogen ions for sodium ions, and when there is a forced secretion of hydrogen ions, as in a primary acidosis, the secretion of potassium may be correspondingly depressed; conversely, in alkalosis the renal output of potassium may be enhanced. (These two effects are opposed in respect of potassium excretion, and the net effect of their balance seems to be that *both* primary acidosis and primary alkalosis can be causes of depletion of potassium.)

3. The administration of potassium salts, even those of strong acids, such as potassium chloride, leads to the formation of an alkaline urine, so that a metabolic acidosis ensues.

4. Cooke and associates[37] have shown that in rats with depletion of potassium the kidneys are handicapped in correcting an extracellular fluid alkalosis, since they cannot form adequate amounts of citrate and oxalacetate in the urine and must thus excrete more chloride. Later work by Evans and colleagues[38] suggests that this phenomenon is much less striking in man than in the rat.

5. Deprivation of potassium, both experimental and clinical, is sometimes, but by no means always, associated with the appearance of an alkalosis in extracellular fluid, as judged by a raised pH and bicarbonate level. This type of extracellular fluid alkalosis is seen particularly when depletion is accompanied by a high intake of sodium of by the

administration of sodium-retaining steroids. It is not primarily of renal origin, for, as it developed in the subjects of Black and Milne,[20] the urine became more alkaline. The best available explanation for the phenomenon seems to be that of Cooke and associates[26] who suggested that the extracellular fluid alkalosis was attended by a corresponding, or indeed greater, acidosis within the cells. This explanation meets the difficulty of understanding how a deficit of cation can lead to an alkalosis, and it is supported by a comparison of balances of sodium, potassium, and chloride during the development and retrogression of experimentally induced hypokalemic alkalosis. Evidence for a similar combination of extracellular fluid alkalosis and intracellular fluid acidosis, associated with depletion of potassium in a clinical situation, has been given by Davies and co-workers.[39] They studied pyloric stenosis in adults, found evidence of depletion of potassium, and showed that the associated extracellular fluid alkalosis disappeared with even alkaline salts of potassium, during which time more metallic cation was retained in the body than anion.

The presence of a lowered hydrogen-ion concentration in the muscle cells of rats depleted of potassium has recently been confirmed by Saunders and associates[40] who found a correlation between hydrogen-ion concentration and potassium content of fat-free dry substance.

More work is certainly needed on this problem in other clinical situations, among which that in infantile pyloric stenosis would be of interest. The findings in adults suggest that with transient vomiting, the alkalosis is "pure," and can be corrected by giving chloride, but in chronic vomiting depletion of potassium becomes prominent and demands potassium salts for the correction of the alkalosis. There are also unsolved problems of the mechanism of production of this type of alkalosis, in particular, the reason for its inconsistency in experimental depletion of potassium,[32] and the reason the kidneys do not dispose of the extracellular fluid alkalosis by secreting a highly alkaline urine. In a discussion of these difficulties, Fourman[41] points out that a high intake of phosphate, as in the milk diet of our experiments, may favor the development of extracellular fluid alkalosis as was observed in rats by Seldin and associates.[42] This idea would be consistent with the view of Black and Milne[20] that change in the valency of intracellular phosphate esters could contribute to the buffering of hydrogen ions within the cells. With relation to the imperfect renal response to the extracellular fluid alkalosis, Fourman also points out that depletion has often been shown to diminish excretion of bicarbonate, possibly because of increased acidity of cells in the renal tubules.

CLINICAL POTASSIUM DEPLETION

Depletion of potassium now has been observed in a considerable variety of diseases and syndromes, some of which are listed in Table II. As has already been mentioned, diminished intake of potassium is, in general, only a contributory factor, unless it is unusually strict and prolonged; by itself, it can only lead to a moderate degree of depletion of potassium. Severe states of depletion are determined by abnormal losses of potassium from the body and these occur in the gastrointestinal tract or in the urine. The theoretical possibility of significant loss of potassium in the sweat under tropical conditions has not yet been explored adequately. Although the list in Table II is classified in terms of the main underlying cause of depletion, it should be remembered that in some syndromes potassium is lost in several ways. For example, the depletion of pyloric stenosis is based in part on loss of intake and of gastric juice and in part on an increased urinary excretion of potassium, itself determined by several causes including wasting of tissue, a low excretion of hydrogen ions, and possibly the influence of aldosterone secreted in response to attendant depletion of sodium.

The listing of a number of states in which potassium depletion has been described does not, of course, indicate the prevalence of

Table II. Some causes of clinical potassium depletion*

A. Deficient intake (usually only a contributory factor)
Anorexia, coma, special diets, vomiting
B. Gastrointestinal losses
1. Vomiting—pyloric stenosis
2. Fistulas—biliary and pancreatic, gastrocolic
3. Continuous aspiration—intestinal obstruction
4. Fecal—gastroenteritis, steatorrhea, ulcerative colitis, abuse of purgatives, mucinous papilloma, ureterocolic anastomosis, use of exchange resins, repeated enemas and washouts
C. Renal losses
1. Secondary to tissue breakdown—malnutrition, dehydration, acidosis, catabolic response to trauma, diabetic coma
2. Action of hormones—primary aldosteronism, Cushing's syndrome, steroid therapy
3. Action of diuretics—cardiac edema, cirrhosis
4. Renal disease. Renal tubular acidosis, renal aminoaciduria, potassium-losing nephritis, nephrotic syndrome treated with diuretics, resins, and steroids

*References to reports of depletion of potassium in these conditions are given by Black.[49]

the depletion since the list is of possible and not of necessary associations. A moderate degree of depletion is very common in sick patients, but causes few if any symptoms. Severe depletion is much less common, but may form a large part of the clinical picture. This is also somewhat different in acute illness and in chronic states of depletion which have come about slowly as a result of sustained moderate loss in stools or urine. The symptoms of depletion are further confounded by the inconstant relation between the magnitude of depletion and the level of plasma potassium; thus the presence or absence of hypokalemia, with its rather characteristic symptoms, cannot be used to infer the presence or absence of significant cellular depletion. Rather than repeat information already given under the headings of hypokalemia, significance of intracellular potassium and experimental depletion, I shall try to indicate in brief compass some clinical features which should arouse the suspicion of significant depletion and the type of evidence which should then be sought to justify treatment with potassium salts, which is not always free from risk.

Acute severe depletion arises in acute disturbances of the alimentary tract when no potassium is ingested and there are massive losses of potassium in vomit and stools. The clinical picture is dominated by concurrent depletion of sodium, which produces clinical dehydration, low volume of plasma, and circulatory collapse; at this stage, the plasma potassium is normal or even raised. When depletion of sodium is corrected by saline infusion, the depletion of potassium is unmasked, the plasma potassium falls, and neuromuscular symptoms may then appear. The patient remains ill and recovers only when potassium balance is restored by intake of food, or more rapidly by potassium salts. In these acute disturbances, depletion may have to be assumed rather than proved, and in infantile gastroenteritis the inclusion of potassium salts in infusion fluids has justified itself by a reduction in mortality rates. The limit to treatment with potassium salts lies in the toxicity of a raised concentration of plasma potassium. This danger is greater during the phase of dehydration and renal inadequacy secondary to depletion of sodium, but ample experience now has shown the value of solutions, such as the "K-lactate" solution of Darrow which is given slowly and preferably subcutaneously.[43]

Chronic severe depletion of potassium is less common than acute severe depletion; it is also more difficult to recognize, or at least it may pass unsuspected for some time, although once suspicion has been aroused there are valid techniques for establishing its presence. Just as acute severe depletion is associated with acute gastrointestinal disturbance, so chronic severe depletion is to be found in chronic disorders of the gastrointestinal tract, with loss of potassium in the feces; in addition it is found in association with prolonged abnormal losses of potassium in the urine, which arise from a renal lesion

or from the effect of adrenal hormones in promoting urinary excretion of potassium. A number of specific causes of chronic depletion have been mentioned in Table II; the range of conditions is so wide and the loss of potassium in any one of them so variable, however, that etiology by itself is of comparatively little help in arousing suspicion of depletion. The clinical picture is also variable, and patients with chronic depletion are often regarded as suffering from "functional illness" for months or even years, in view of their complaints of anorexia, lethargy, and weakness. Episodic weakness, occurring at night or an hour or two after a heavy meal, may suggest depletion more definitely than does continuous weakness. Patients with depletion often complain of thirst, and this is not merely a consequence of the polyuria from which many of them also suffer.[44] The investigation of hypertension occasionally reveals patients with primary aldosteronism, and the association of hypertension with hypokalemia and an alkaline urine always calls for critical study. Fortunately, the plasma electrolyte concentrations are more likely to be abnormal in chronic depletion of potassium, which is relatively uncomplicated by dehydration, than they are in acute depletion; the finding of hypokalemia or of a raised plasma bicarbonate is useful confirmation of a clinical suspicion that depletion is present.

When depletion seems likely on the type of evidence which we have outlined, further study is needed to establish the cause, the route of loss, and the magnitude of loss, on which maintenance treatment with supplements of potassium will ultimately depend. The decision on the cause rests mainly on general medical investigation, but it can be assisted by establishing whether potassium is being lost in the stools or in the urine, or, of course, in some other obvious way, as by fistula or by prolonged vomiting. In those patients, and they are a majority, in whom the plasma potassium is below 3.5 mEq. per liter, there should be very little potassium in the urine if the route of potassium loss is extrarenal; on the other hand, the finding of a urinary concentration of potassium above 20 mEq. per liter in these circumstances is strong evidence of a urinary loss of potassium, which in turn calls for investigation of renal and of adrenal function. In those patients who have a plasma potassium within the normal range, the route of the loss can be established by putting them on a diet with restricted content of potassium, for instance, 20 mEq. per day, and observing whether the urinary output of potassium is in excess of this; the amount of potassium lost in the urine under these conditions is a useful guide to the amount of supplement which will be needed in those patients with primary renal disease whose loss of potassium cannot be directly controlled. When the route of the loss is fecal and the primary condition cannot be controlled, the quantitation of loss calls for full balance study, with estimation of fecal potassium, whose amount is again a guide to the amount of additional supplement needed. Where the necessary supplement has been established, it can be given by mouth in the form of potassium bicarbonate or citrate. These "alkaline" salts of potassium are less unpalatable than potassium chloride, and they are also more appropriate in renal acidosis or for the correction of the intracellular acidosis of depletion. Direct observation of urinary or fecal losses of potassium seems to me preferable to inferences from the results of muscle biopsy or determination of exchangeable potassium, in that they are a more direct guide to the amount of additional potassium which will be required.

Some of the conditions mentioned in Table II, e.g., anorexia, diabetic coma, and diuretic treatment, are the cause of moderate depletion only. This condition is difficult to recognize and to establish, and it is not usually of great importance in the whole clinical picture. However, in special circumstances it may be significant. For example, the postoperative depletion of potassium can usually be neglected, but in patients who lose fluid, or who fail to eat, a more significant depletion may develop, of which the catabolic response to an operation is a con-

tributing cause. Again, moderate depletion of a degree which normally causes no symptoms may lead to digitalis toxicity in the patient with cardiac failure. In general, however, deficits of potassium which are not causing either symptoms or definite biochemical abnormalities can be neglected reasonably.

CLINICAL POTASSIUM EXCESS

We have used the word "excess" as a natural contrast to "depletion," but "intoxication" might be a more appropriate term, since the symptoms of overdosage with potassium are due to increased concentration of potassium in extracellular fluid and can therefore occur when the whole body content of potassium is normal or even reduced; an important practical consequence of this is that they can arise during the repair of a depletion if potassium salts are given too rapidly. Retention of potassium in the body, with the possibility of a rise of plasma potassium to toxic levels, is found in acute renal failure (tubular necrosis), occasionally in chronic renal failure, and in states of deficiency of aldosterone which may not be limited to classical Addison's disease.[45] The recognized signs of an excess of potassium are those of hyperkalemia, which have already been outlined. When the circumstances suggest hyperkalemia, the serum potassium must be estimated, and serial E.C.G. tracings obtained, so that there may be early warning of cardiac disturbances. Prevention of a rise in serum potassium is an essential part of the general management of acute renal failure.[46] When retention of potassium depends on adrenal insufficiency, it can be corrected by deoxycortone or fludrocortisone. In an emergency, serum potassium can be lowered acutely by infusion of alkaline sodium, e.g., molar lactate 40 ml., or by insulin and glucose.

Finally, it should be emphasized that clinical disturbances of potassium metabolism are always attended by alterations in other electrolytes, as indicated, for example, in the section on alkalosis associated with depletion of potassium. Potassium-centered management, like patriotism, is not enough; these problems must be considered in the wider context of general electrolyte and nutritional disturbances. General problems of this type have recently been discussed in relation to pediatrics by Talbot and co-workers[47] and by Darrow.[48]

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Volume and composition of the body fluid compartments in severe infantile malnutrition

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VARIOUS alterations in the composition of the body fluid compartments during states of malnutrition have been reported. These have consisted of changes in the volumes of the body fluid compartments and in the concentrations of their constituents. The present study reports observations of the body fluids in groups of children malnourished from various causes. These children were studied for evidence of: (1) expansion of extracellular volume in relation to body weight, (2) edema formation, (3) alteration in the concentrations of certain blood constituents, and (4) the circulatory and metabolic sequelae during dehydration from diarrhea.

CASE MATERIAL

The patients were infants and small children who were classified in the following four clinical groups based on the cause of their malnutrition.

Group I. Severely malnourished children with edema (20 cases). These infants were from a population of gypsies of poor economic circumstances, who do not seek pediatric care. The age range was 1½ to 3 years. Their weights on admission averaged 35 per cent below normal for their respective ages. The clinical histories indicated a very poor intake of protein. Clinically, the children resembled those seen with kwashiorkor except for the absence of or less pronounced signs of skin and hair involvement.

Group II. Severely malnourished children without edema (10 cases). The age range and degree of malnutrition were similar to those in Group I. However, the origin of malnutrition was not primarily due to lack of dietary protein, but it was associated with low caloric intake, poor hygiene, and frequent infections.

Group III. Severely malnourished infants with dehydration (14 cases). The average age in this group was 3½ months. The clinical histories of malnutrition were similar to those of the children in Group II. Dehydration was associated with a bacterial enteritis and was characterized by rapid loss in weight, disappearance of subcutaneous fat depots, and a tendency to hypothermia. When death occurred it often appeared to be due to a central respiratory paralysis.

Group IV. Well-nourished infants with dehydration due to diarrhea (11 cases). These patients, clinically, exhibited severe dehydration, circulatory shock, and acidosis.

METHODS

Serum protein determinations were done by fractionation of the albumin and globulins with sodium sulfate and by Kjeldahl

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determination of the protein nitrogen. Colloid osmotic pressure of the serum was calculated from the formula of Keys.[23] Venous pressure was measured in an arm vein, manometrically. Enzyme activity of duodenal fluid was analyzed by the procedures of Freudenberg.[8] Oxygen consumption of the patients was measured by spirometry. Oxygen content of venous blood, obtained from the sagittal sinus, was determined volumetrically by the method of Van Slyke. Circulation time was determined from the time required for Congo red injected in an arm vein to appear in the blood of the sagittal sinus. Serum concentrations of sodium and potassium were determined by flame photometry. Blood sugar concentrations were determined by the technique of Hagedorn and Jensen.[14] "Extracellular" body fluids were measured by the thiocyanate method.[15]

OBSERVATIONS AND DISCUSSION

1. Expansion of extracellular volume in relation to body weight. The expansion of extracellular fluid volume relative to body weight has been a constant feature in previous reports of malnutrition in adults[2, 3, 23, 29] and infants.[10, 15] The main cause of this relative expansion of the extracellular space appeared to be the result of disproportionate losses in the body structures. The skin, nervous tissue, and skeleton of the body did not change much with loss in body weight. However, these structures contained a considerable proportion of the extracellular fluid. The major losses of body weight in malnutrition resulted from losses of fat and protoplasmic mass,[15, 16] which contain relatively little extracellular fluid in the case of fat tissue and none in the case of protoplasm. This relative increase in extracellular fluid has been considered "occult" edema,[2] but we would reserve the term edema for those instances in which the extracellular fluid undergoes an absolute increase in volume over the volume the individual would have had were he not malnourished. The physiologic significance for this distinction between an absolute and relative change in the volume of extracellular fluid was illustrated by our observations on malnourished infants who were studied when they suffered from malnutrition alone, and again after they developed dehydration from diarrhea. The extracellular space in these malnourished children increased relative to their observed body weights before, and even after, they developed diarrhea. During the diarrhea, however, the extracellular space was decreased relative to the ideal or expected body weights for these patients. During diarrheal episodes, these patients exhibited elevated hematocrits, prolonged circulation times, and low renal clearances, which are characteristic of patients with hypovolemia. Thus the absolute fluid volume of the extracellular space, rather than its size relative to the body weight, is the important factor in maintaining normal homeostasis in malnutrition.[7]

2. Edema. Edema, i.e., an absolute increase in volume of the extracellular space above the normal value for expected body weight, was not a constant feature in the malnourished infants and children. It was present in only 2 per cent of the infants studied who were less than 1 year of age and in 12 per cent of the malnourished children. In the 20 cases from Group I, the edema was most conspicuous in the lower extremities and of lesser degrees in the hands and face. None of the patients had ascites.

The edema disappeared usually within 10 days after the institution of corrective dietary measures.

Some of the results of the studies conducted on the patients suffering from malnutrition with and without edema are presented in Table I.

The genesis of the edema in malnutrition can be partially explained in terms of the Starling hypothesis. Hypoalbuminemia was consistently found in our cases of malnutrition with edema as has also been observed in kwashiorkor.[5, 9, 11, 34] The calculated osmotic pressure was one half the normal value in the edematous patients. It was not significantly altered in the nonedematous ones, although the severity of the malnutri-

Table I. Serum proteins, colloid osmotic pressures and cholesterol concentrations in 20 edematous (Group I) and 8 nonedematous (Group II) patients with malnutrition

Patients	*Total protein (Gm. %)*	*Albumin (Gm. %)*	*Globulin (Gm. %)*	*Colloid pressure (mm. H_2O)*	*Cholesterol (mg. %)*
Edematous	4.22 ± 0.63	2.34 ± 0.45	1.81 ± 0.5	146 ± 35	89.5 ± 15
Nonedematous	7.1 ± 0.90	4.13 ± 0.62	2.95 ± 0.68	317 ± 61	–
Normal	7.2 ± 0.55	4.80 ± 0.41	2.40 ± 0.59	351 ± 33	220 ± 32

tion in the two groups was identical. This striking difference between patients of Groups I and II suggested the following conclusions: (1) From the clinical histories and the data of Table I, it was apparent that hypoproteinemia was not a necessary consequence of malnutrition per se, but only so when the malnutrition resulted from low intake of protein or from poor intestinal absorption of it. (2) In the young age groups, when malnutrition occurred without hypoproteinemia, malnutrition was not a decisive factor in the genesis of edema. In contrast, semistarved adults with normal or only slightly reduced serum protein concentrations have been observed to develop edema in the lower extremities.[2, 29] This contrast between adults and infants may be related to differences in muscular activity, environmental exposure, or postural factors in the two age groups. It should be emphasized that the nonhypoproteinemic edema of the semistarved adult is an isohydric edema[2] which appears without any or with only a slight increase in the absolute volume of the extracellular fluid.[29] (3) The essential role of hypoproteinemia for edema formation may explain the differing incidences of edema in malnutrition from different countries. In the tropical countries, where edema is most frequent, low protein intake has been the major factor in malnutrition.

In order to realize the importance of hypoalbuminemia to edema formation in malnutrition, an explanation is necessary for the fact that edema appeared in patients with malnutrition at higher serum albumin concentrations than in patients with nephrosis (Fig. 1). In most patients with malnutrition and edema, the serum albumin concentrations were between 2 and 3 Gm. per cent, concentrations at which most nephrotic patients are edema free. A similar situation has been described by Weech, who studied edema formation in dogs that were malnourished by protein-deficient diets and in dogs depleted of plasma proteins by plasmapheresis.[36] The differences in edema formation were explained from the observations that the malnourished dogs also had wasting of the subcutaneous structures and loss of elasticity of the skin. The consequent loss of tissue turgor rendered the subcutaneous tissues of the malnourished dogs less resistant to fluid accumulation than the same tissues of the well-nourished dogs subjected to plasmapheresis. These results may explain why edema formation occurs at different serum levels of albumin in association with malnutrition from those with nephrosis. In nephrosis, the degree of body wasting is less severe.

In the Starling hypothesis, an elevated venous pressure is next in importance to the low colloid osmotic pressure of the plasma for edema formation. Keys[23] observed low venous pressures during uncomplicated semistarvation in adults and concluded that "the occurrence of edema coincided with changes in venous pressure, but in the opposite direction to that expected." A decrease in venous pressure might counterbalance to some extent the edema-promoting effect of hypoproteinemia. A contributory role of venous pressure in edema formation has been seen when the venous pressure was studied after muscular activity, rather than at rest. Under these circumstances, Govaerts and Léquime[12]

found a sharp rise in venous pressure in semistarved adults. In our 10 cases of severely malnourished infants, most of them edema free, low venous pressures in the arm veins were observed. The pressures were 45 ± 15 mm. of isotonic saline solution whereas 7 normal infants had pressures of 103 ± 14 mm. of saline. In 2 of our patients, however, who had serious intercurrent pneumonia the venous pressures were elevated to 230 and 240 mm. of saline, respectively. In a third patient, venous pressure was elevated after plasma infusions. This patient was a malnourished child with edema. An attempt was made to relieve the edema by increasing the plasma colloid osmotic pressure by infusions of plasma. The results of such therapy on the circulatory system are illustrated in Fig. 2. As expected, the colloid osmotic pressure of the plasma did increase, but the venous pressure rose to twice the normal value, and the cardiac output and inulin clearance were sharply reduced. The acute expansion of the plasma volume had evidently overburdened the heart, producing an elevated venous pressure similar to that seen

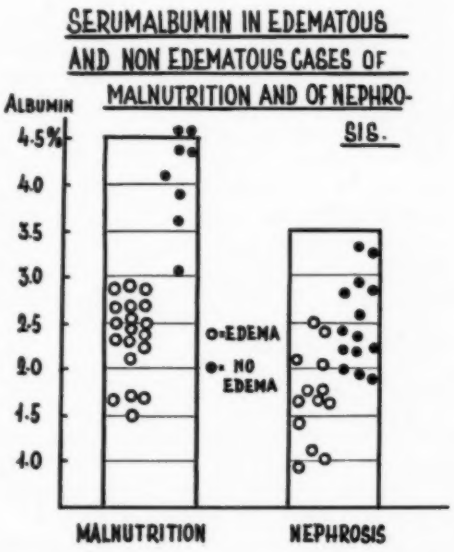

Fig. 1. Comparison of serum albumin concentrations in patients with edema from malnutrition and nephrosis.

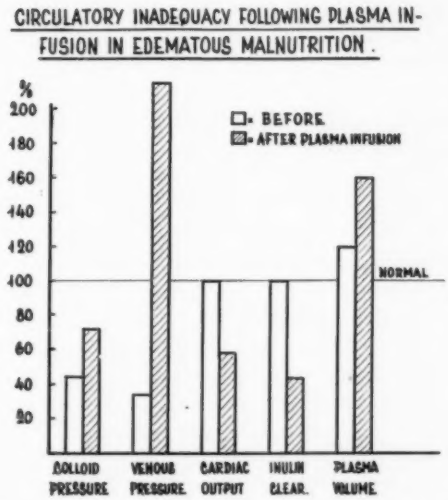

Fig. 2. Comparison of the circulatory events that occurred after plasma infusions to a patient with edema from malnutrition and to normal patients.

in the patients above with pneumonia, and also observed after muscular activity[12] and in starved patients whose repletion by food is too rapid.[23] These diverse factors may tend to increase water retention, which may result in elevated venous pressures if the heart is abnormal. In reference to the heart, it has been observed that cardiac muscle is also involved in wasting processes (such as malnutrition) that affect skeletal musculature.[16, 23, 24] Cardiac output is also known to be low in the semistarved adult[12, 23] and in severe malnutrition.[7]

Since the pathogenesis of edema in many diseases is now known to be a complex process, the Starling hypothesis of fluid equilibrium is only one link in a chain of events leading to edema. As mentioned above, other circulatory factors may contribute to the formation of edema in malnutrition. Renal and humoral factors have not been adequately studied in this type of edema. Renal clearances are low in kwashiorkor,[11] but may also be reduced in severe malnutrition without edema.[17]

No data are available as yet on aldosterone production in this form of edema. Consequently, until more information is

available on the relationship between sodium excretion, circulatory functions, and hormonal secretions, one can only state in reference to formation of edema in malnourished infants and small children that: (1 there is an associated low plasma colloid osmotic pressure; (2) the loss of subcutaneous structures and skin elasticity play a role; (3) in certain instances the mechanisms of "backward" and "forward" cardiac failure may be involved in the retention of water from overburdening of the atrophic heart.

Malnutrition due to protein starvation has, besides edema, other characteristics. Enzyme activities of duodenal juice have been reported to be reduced[11, 28, 33-35] and fatty changes of the liver have also been found in these patients.[1, 11, 34] In Table II are shown the amounts of duodenal lipase and trypsin activity found in patients of Groups I and II types of malnutrition and similar data for nephrotic and normal children.

It is clear from the results shown in Table II that low enzyme contents in duodenal juice were found only in those patients whose malnutrition was due to poor intake of protein.

Hypofermentia of the degree seen in Group I patients has been observed only in the duodenal juice of patients with acquired or congenital fibrosis of the pancreas.[30]

The lipase values shown for the nephrotic children were in the low normal range, but too few cases have been studied for any conclusive statements. All the edematous malnourished patients had a normal thymol test. The low serum cholesterol values for all of the Group I patients (Table I) were in striking contrast to the levels seen in nephrosis.

3. Abnormal electrolyte patterns. In Table III are shown the serum selectrolyte concentrations of 10 of the Group I patients.

Hyponatremia, although reported in patients with kwashiorkor,[4, 7, 9, 32, 34] was not always present in our patients with edema due to protein deprivation. Normal serum sodium concentrations were also found in the edematous malnourished children from Uganda studied by Heller and Schnieden.[13] Also shown in Table III are the low values found in the blood nonprotein nitrogen. The normal NPN for our laboratory is 24 ± 5 mg. per cent. We have previously observed low NPN values in puppies fed low-protein diets.[18]

The discrepancies in relation to hyponatremia observed in various studies of patients with edema from malnutrition may be partially due to differences in salt intake. There is a tendency to hyponatremia in all types of chronic edema, which often becomes manifest with restriction of dietary salt or with the use of diuretics. Hyponatremia has been reported in association with edema in nephrosis,[25, 26] in cardiac failure,[25] and in liver disease.[27, 31] We have also noted hyponatremia in puppies fed a low-protein, low-salt diet. The hyponatremia did not occur if either protein or salt were added to the diet.[18] Evidently the sodium and water regulatory mechanisms, which maintain a normal serum sodium concentration, when salt is restricted in normal individuals, are less precise in clinical disturbances which have a propensity for formation of edema. Observations pertinent to the altered sodium and water regulation have been made by Frenk and associates[7] in Mexican children

Table II. Duodenal enzymes and thymol reaction in edematous (Group I) and nonedematous malnutrition (Group II)

Patients	*Number of cases*	*Trypsin units*	*Lipase units*	*Thymol reaction*
Edematous	14	200 ± 61	1.2 ± 1.7	2.0 ± 0.68
Nonedematous	10	1280 ± 784	7.4 ± 2.0	–
Nephrosis	4	1260 ± 905	3.7 ± 2.0	–
Normals	6	1920 ± 905	7.5 ± 1.7	–

with edema who developed diarrhea. These investigators observed that diarrhea in these children resulted in dehydration and hyponatremia of the extracellular fluid and in an associated swelling of the tissue cells. Such an occurrence, these authors believed, was related to the high mortality rates associated with intercurrent diarrhea in malnourished infants.

Table III. Serum electrolytes in malnutrition associated with edema

Serum Na (mEq./L.)	140.2 ± 5.6
Serum K (mEq./L.)	4.1 ± 0.98
Serum Cl (mEq./L.)	103.8 ± 6.3
Nonprotein nitrogen (mg. %)	14.7 ± 5.7

4. Effects of dehydration. The losses of water and electrolytes consequent to diarrhea was one of the most frequent and dangerous complications that occurred in the children with severe malnutrition of both the edematous and dry types. Diarrhea in these malnourished infants produced changes that are not seen in previously normal infants.

The principal danger of diarrhea in well-nourished children arose from the rapid depletion of extracellular volume. When the extracellular volume was reduced, the circulation time increased, causing a stagnant anoxia. In a previous report, we attributed the semicomatous "toxic" condition, which is so characteristic of severe dehydration which occurs acutely in infants, to cerebral anoxia from reduced cardiac output.[22]

Table IV shows the oxygen consumption, circulation time, and oxygen saturation of the blood in normal infants and in infants with diarrhea who were either normal or malnourished when they developed diarrhea.

When acute dehydration developed from diarrhea in previously normal infants, the oxygen consumption was normal, but the circulation time was increased to twice the normal value. Consequently, the oxygen saturation of the cerebral venous blood was one half the normal value. These infants were in a "toxic" semicomatous state. With further decreases in cardiac output and in cerebral blood flow, these infants, agonally, were observed to have a stagnate anoxia of such a degree that oxygen was virtually absent from the cerebral venous blood. In neglected cases with such dehydration, the infant would die of cerebral anoxia.

The circumstances of death were different when dehydration developed in semistarved infants with pyloric stenosis or with severe malnutrition. Death due to acute shock with associated cerebral stagnant anoxia was less frequent. Dehydration in the malnourished infant followed a more chronic course. In 10 cases studied (Table IV) the oxygen consumption was 40 per cent lower than that of the normal or toxic infants. These infants

Table IV. Effects of dehydration in normal and in extremely malnourished infants

Patients	*Number of cases*	*O_2 consumption (cm.³/1.73 M²)*	*Circulation time (seconds)*	*"Sinus" O_2 Saturation (%)*
Normal	5	242 ± 29	11 ± 2.2	51 ± 4.3
Dehydration in well-nourished infants	7	244 ± 41	22 ± 5.7	23 ± 5.4
Premortal, well-nourished infants	4	–	54 ± 11	2.5 ± 2.3
Dehydration in malnourished infants	10	146 ± 13	36 ± 13	37 ± 10
Premortal, extremely starved infants	4	–	49 ± 8	51 ± 15

Table V. Hypoglycemic attacks in 10 extremely malnourished infants

Blood sugar (mg. %)	19 ± 4.6
Respiratory rate	10 ± 8
Pulse rate	71 ± 18

showed a prolonged circulation time, and the oxygen saturation of the cerebral venous blood was reduced, but not nearly as much as in the other infants. Because body metabolism is greatly reduced in prolonged starvation and in hypothermia, these infants apparently tolerated the prolonged circulation time without developing a stagnant anoxia. Four infants admitted in a terminal condition had normal oxygen saturations despite a fourfold increase in the circulation time.

In the malnourished infant, the danger of diarrhea arises from the further decrease in absorption of food from the gut,[19] and the concomitant loss of calories in the stool. These latter events, added to the depletion of fat stores, lead to more rapid wasting of body tissues and extreme starvation. In 10 such infants (Table V), a marked hypoglycemia was found when they became moribund. The hypoglycemia was associated with alarming symptoms. The infants developed sudden pallor and coma, followed by slowing of the pulse and of the respiratory rate and even by apnea.[21]

It appeared that the main threat of diarrhea in the malnourished infant was starvation to such a degree that the tissues were unable to provide substrate for vital processes. In these 10 malnourished infants, intravenous 20 per cent glucose administration reversed 16 of 18 of these hypoglycemic apneic attacks with restoration of the pulse, color, and respiration. The subsequent rehabilitation of these athreptic infants was accomplished by the initial use of glucose and saline infusions and ACTH.

SUMMARY

The following observations were made in infants and children suffering from malnutrition of different causes:

1. A percentage increase in extracellular fluid volume in relation to the actual body weight was the only consistent change in the extracellular fluid compartment.

2. The occurrence of edema (i.e., absolute volume expansion of extracellular fluid) was associated only with malnutrition due to low protein intake. In patients with edema, hypoproteinemia and reduced enzymatic activity of the duodenal juice were invariably observed.

3. The important factors leading to formation of edema in malnourished infants and children were a decrease in plasma colloid osmotic pressure and a loss of skin elasticity. Ineffective cardiac and perhaps renal compensatory capacities in these malnourished children were thought to contribute to formation of edema when there was too rapid expansion of the intravascular volume by infusions of plasma, intercurrent infections, or overfeeding.

4. The occurrence of diarrheal disease in patients with malnutrition may cause hyponatremia or cerebral anoxia from circulatory shock. These alterations were, however, less common than in normal infants suffering from diarrhea. Because of lower body metabolism in malnutrition, such infants were better able to withstand the circulatory stasis and anoxia. These patients had an accelerated wasting of body substance in diarrhea because they had no caloric reserves from which to draw during a period of decreased food assimilation. Malnourished infants were subject to death from sudden hypoglycemia resulting in respiratory paralysis.

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THE PATIENT (aged 7 years and 8 months) was well until 5 days prior to admission, when he developed frontal headaches while at school. Despite a continuing headache, he went to school where he seemed lethargic and vomited several times. One day prior to admission he was seen by his physician for the headache, vomiting, and lethargy. On the day of admission, lethargy increased and he slept most of the day. Past history revealed that 3 weeks prior to admission the patient had an ear infection which had been treated with antibiotics; 1½ months prior to admission he had suffered a fall while skating but there had been no loss of consciousness. In retrospect, the parents thought that mild headache may have been present intermittently for about 6 months. There was no complaint of vertigo, and change of position was not known to influence his symptoms. Pica and enuresis were denied.

The patient was born at full term after a normal pregnancy and delivery. His appetite is good. He is in the second grade at school. The family (3 siblings) are all well. The father is a plumber.

On physical examination he was found to be somnolent, well developed, and well nourished, and in the 90th to 98th percentile for weight. Temperature was 100° F., respiration, 20 per minute, pulse 65 per minute, and blood pressure, 110/70 mm./Hg. The head appeared large (57 cm. in circumference). Normally reacting pupils and normally mobile eyes with slight nystagmus, bilateral papilledema, and bilateral fundic hemorrhage were noted. Ears, nose, and throat were normal. Other cranial nerves were intact. He spoke slowly when awakened but was well oriented. He had good motor function except for mild nonlocalizing instability of gait. Toe signs were down. Deep tendon reflexes were unobtainable except at the right ankle and knee (1 plus).

Urinalysis revealed a specific gravity of 1.035, no albumin or sugar, acetone 2 plus, and sediment negative. Blood hemoglobin was 13 Gm. per cent. White blood cell count was 17,000 with 68 per cent polymorphonuclear leukocytes. Total protein of ventricular fluid on the day following admission was 43.2 mg. per cent. There was no growth on culture of the ventricular fluid. No cells were found in the fluid. Serum sodium on the sixth hospital day was 129 mEq. per liter and increased with treatment to 135 mEq. per liter on discharge. Tuberculin (1:1,000) was negative. Anteroposterior and lateral views of both knees were normal.

On the evening of admission the patient's pulse and respiratory rates were slow. He was watched closely over the first 7 hours following admission with no change in his heart rate or mental status. At 7 A.M. on the first morning after admission the patient sud-

denly became extremely lethargic, nearly unresponsive, and incoherent. Pupils became dilated and fixed. Respirations decreased. He was placed on emergency ventricular drainage. Following the insertion of ventricular drainage, the patient immediately became more alert and responsive, and his pupils began to react to light and accommodation. He was watched closely for the next 2 days. There was steady improvement in his condition and complete loss of the headache. On the third hospital day air was injected into the right ventricular cavity. This ventricle was enlarged and extended across the midline anteriorly where there was a lobulated soft tissue density along the right ventricular floor. Only a minute bubble of air passed from this ventricle and could be seen in the posterior portion of the third ventricle. No other air was demonstrated. An operation was performed.

DR. RICHMOND PAINE.* The story is clearly one of cerebral disease, probably with increased intracranial pressure, since he improved dramatically with ventricular drainage. Immediately we think of tumor, abscess, encephalitis, poisoning (particularly lead) and more remotely, tuberculous meningitis, and so on. The short history scarcely fits any one of these diagnoses well, although a space-taking lesion may produce dramatic symptoms by sudden obstruction of cerebrospinal fluid flow or by sudden pressure on a blood vessel.

I believe there are a number of irrelevant factors which must be sorted out. Almost everyone has upper respiratory infections, bumps his head, and does not have any symptoms with change in head position, the latter sign being classic for intermittent obstruction of the foramen of Munro, but, in my experience, rarely seen. Of more value would be information about change in symptoms when he strained at stool. Abscess, either secondary to respiratory infection or to fracture (as of the cribiform plate), heads my list of possibilities, despite relative lack of fever or leukocytosis, normal ears, and despite absence of cells in spinal fluid. The general course is unlike the ordinary subdural hematoma. We have nothing to indicate pituitary involvement, although his somnolence may be due to hypothalamic involvement. The relative bradycardia probably is equally nonspecific and arises in association with increased intracranial pressure.

His head is large, probably from chronic increase in intracranial pressure, but one would want to know his father's hat size as well. One must suppose that the instability of gait was not true ataxia and decide whether the variation in reflex activity (the asymmetry makes it impressive) reflects abnormality of the right or left side; probably in this case the left side is abnormal and therefore cerebral lesions would be on the right side. Paradoxical hemiparesis may result from compression of the opposite cerebral peduncle against the tentorium and throw us off the track.

If he has a space-taking lesion, such as a tumor or an abscess, it is likely to be in the temporal lobe. Dysphasia, often present with left-sided lesions, might be overlooked on casual examination, but if the lesion is right-sided even this sign would be lacking. Easily overlooked quadrantic deficits of visual fields and possible uncinate seizures also may occur with temporal lobe lesions.

Even though porphyrin determinations were not made, the negative history of pica and adequate school progress, absence of albumin and sugar in the urine, lack of anemia, and normal x-ray of long bones adequately exclude lead poisoning. Determinations of urinary coproporphyrin would be of little help in this case since they may increase with encephalitis and with cerebral tumors. Whether they arise from breakdown of hemoglobin or of nervous tissue seems to make little difference with ordinary methods of determination.

Early in the morning after admission, the midbrain had clearly herniated through the tentorium or the medulla through the foramen magnum or both. Immediate emergency

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Fig. 1. The right lateral ventricle is displaced across the midline. There is a lobulated mass protruding from the floor of this ventricle. The left lateral ventricle is not seen. There are some signs of chronic increase in intracranial pressure.

ventricular drainage provided a singularly fortunate result, since decompression was accomplished before irreversible changes occurred.

Obviously the x-ray will provide the major clue to diagnosis here. One would like to know whether there were abnormalities of the mastoids or ears, whether there was intracranial calcification and erosion of the sella, or whether there were signs of long-standing increase in intracranial pressure. One wonders why the air was injected into the right lateral ventricle. Had he developed new localizing signs or did the reflex findings in the left leg appear to indicate a right-sided lesion?

DR. DONALD B. MATSON. The right side was used for ventricular drainage as a matter of convenience.

DR. PAINE. The x-ray, then, shows a swelling in the floor of the enlarged and leftward-shifted right ventricle. We do not know about the left ventricle because it did not fill. It could be large or small, although the smallest ventricle is often (but not always) on the side of a space-taking lesion. There is very little air in the third ventricle and possibly something is pressing down on it from above.

If this is not an abscess, what is it? Astrocytoma is most commonly found and may often, although not necessarily, be calcified. Also, it would usually have a single smooth and not lobulated contour if it were cystic. Ependymomata, on the other hand, lie more commonly close to the ventricle, are often lobulated, and need not be calcified. There are two points against an adenoma of the choroid plexus: usually there is a communicating, not an obstructive, hydrocephalus, and second, if they occur in the lateral ventricle, they originate from the glomus and not so far anteriorly as this lesion. The attractive possibility of a colloid cyst of the third ventricle would not give a lobulated outline. Usually other supracellular lesions are midline in position and the vast majority are calcified, but a laterally placed dermoid or epidermoid cyst may occur. Some people believe that these have (in air x-rays) a curious irregular streaking arrangement corresponding to the folds of the surface, which is pathognomonic of this lesion.

Facts strongly in favor of abscess or other, possibly mycotic, infection really are limited to the history of respiratory disease. Similarly, if an intracranial hemorrhage produced this bulging mass, I should think one could expect cells in the cerebrospinal fluid.

Finally, I think that we are dealing with a tumor of the floor of the lateral ventricle and that the acute symptoms result from obstruction at the foramen of Munro or anterior part of the third ventricle. Dr. Harris can probably tell us what type of tumor this is from the x-ray, but it would not be fair to ask.

DR. GEORGE B. C. HARRIS. The lateral plain film of the skull shows the split sutures. The

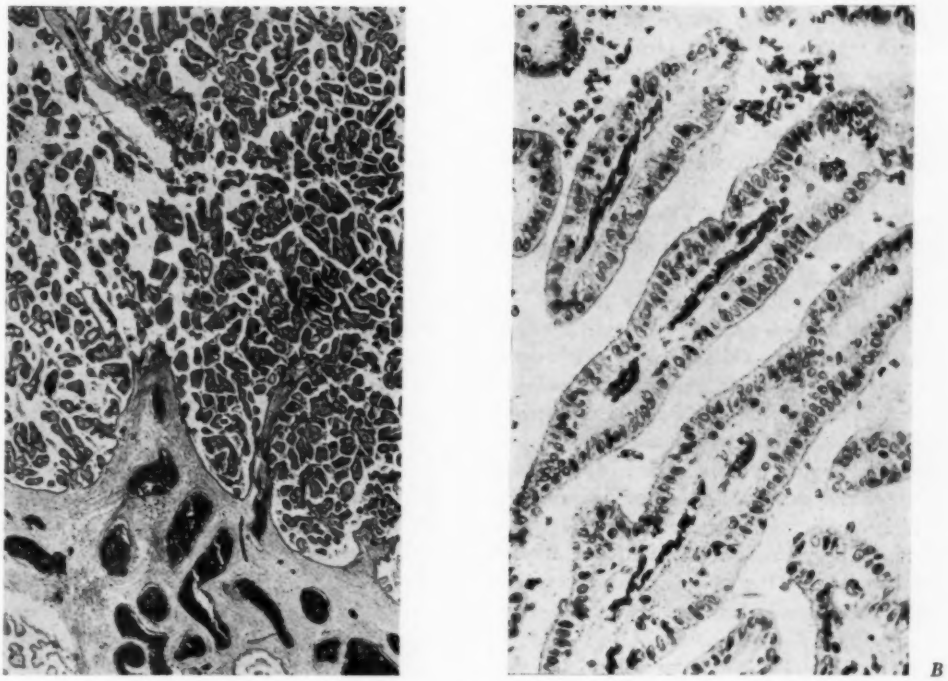

Fig. 2. *A* and *B*, High and low power microscopic views of papillary adenoma of choroid plexus. (Toluidine blue and eosin. ×50 and ×160.)

head is perhaps a little large, but there are no localizing signs in this film, such as calcification or erosion of the sella turcica. One feels that the thinning of the cranial vault and the width of the sutures may indicate chronically elevated intracranial pressure.

In the frontal view (Fig. 1) in the ventriculogram, the large right ventricle is shifted toward the midline, almost certainly under the falx cerebri. The floor of this ventricle contains the lobulated tumor.

DR. PAINE. Perhaps I could be permitted a parting shot. The x-rays indicate a long-standing intracranial hypertension and the appearance of the mass, which may be almost pedunculated, is precisely that of a choroid plexus adenoma, although it lies quite far forward, apparently.

DR. MATSON. This case is unique in several ways. One cannot count on being as lucky as this when acute intracranial hypertension develops, and thinks that sufficient warning of impending disaster was given by the patient at the time of admission to prompt more energetic treatment of this condition. It is fortunate that someone like the neurosurgical resident happened to be near the bedside when this acute accident occurred. Also, the fact that sterile surgical equipment, required for a drill-hole decompression of the ventricle, was immediately available, probably saved this boy's life.

We felt, partly on statistical grounds, that this boy probably had a lesion in the posterior fossa, until the ventriculogram showed a mass protruding into the lateral ventricle. Statistically, this means ependymoma to me.

Unlike the adult, where the fourth ventricle site is most common, choroid papillomas in children occur most often in the posterior part of the lateral ventricles near the glomus.

We thought that failure to fill the left lateral ventricle with air probably occurred because that ventricle was filled with tumor. Therefore we explored the left side first, only to find it normal except that the septum pellucidum ballooned over from right to left. When this was incised, we found the tumor in the anterior aspect of the right ventricle which had prolapsed through the foramen of Munro.

DR. GORDON F. VAWTER. The tumor is a *papillary adenoma of the choroid plexus.* It was fleshy, very soft, and pink, with rugose surface and measured almost 3 cm. in diameter. Typically, the papillary fronds were lined by a single layer of nonvacuolated or nonciliated cells lying upon an often degenerate and calcified fibrovascular core in which no glial tissue was seen (Fig. 2). This kind of degeneration probably has a good deal to do with the tendency of these tumors to produce massive intraventricular hemorrhage.

DR. MATSON. It is a happy thing to be able to give a 2-year follow-up at a C.P.C. The boy recovered quickly from the operation and has remained completely well.

This choroid papilloma fascinates many people even though it is not too common. Geneticists are interested because this may be a congenital lesion: we have seen them in newborn infants and have removed one from a premature infant 3 weeks before the expected date of confinement. The physiologist is interested in these tumors because they are associated with hydrocephalus in the complete absence of block to the circulation of cerebrospinal fluid. Pathologists are interested in the tumor because of its relation to other ependymal tumors and because of the rare possibility of malignancy. The pediatrician is interested because they are so common, relatively speaking, in early life. Finally, they are of interest to the surgeon because in most instances a surgical cure can be obtained if they are diagnosed early enough.

In 17 years we have seen 16 cases; most are in children under 3 years of age, the average age being 14 months. The characteristic picture, if there is one, is that of increased intracranial pressure, communicating hydrocephalus, often with xanthochromic or bloody cerebrospinal fluid with high protein content, and a mass in the lateral ventricle. All 16 tumors occurred in the lateral ventricles except for one which occupied the fourth ventricle. Only one other case is known to me in which the papilloma arose in an area similar to that in which today's tumor was found. Many of them have been quite large, up to 8 cm. in diameter. In the 11 patients in whom they were successfully removed (7 are normal and 4 are somewhat retarded), the hydrocephalus has been cured, and therefore it seems unlikely that the hydrocephalus results from block of the resorbing mechanisms secondary to intraventricular hemorrhage.

COMMENTS ON CURRENT LITERATURE

The etiology of cat-scratch fever

CAT-SCRATCH fever, benign lymphoreticulosis, is a nonfatal systemic illness typified by malaise, headache, low grade fever, and lymphadenitis. While the patient may not appear acutely or chronically ill, the characteristic lassitude can be so marked as to be alarming, and the size of the involved node or nodes is often striking. In most instances the history will reveal some association with cats, although the patient may not recall the time or location of a specific abrasion. The incubation period is variable; a survey of cases described in the literature has indicated an interval of from 10 to 30 days between the date of probable inoculation and the development of significant regional adenopathy. In 1 volunteer subject inoculated intradermally with material from the node of a known case of cat-scratch disease, regional adenopathy began 8 days following inoculation and progressed to fluctuation in about 20 days.[1] At the height of the response of the lymph node a skin papule appeared at the site of the primary intradermal inoculation and persisted for several days. This sequence observed in a human subject infected experimentally seems to be characteristic also of the natural infection.

Apparently the disease is of world-wide distribution, having been reported in France, Great Britain, Canada, Australia, the United States, South America, Switzerland, and India. Viral etiology has been postulated, the agent thought to belong to the psittacosis-venereal lymphogranuloma group. Patients with this disease show low titers of complement-fixing antibodies to Lygranum and positive skin reactions following intradermal injection of an antigen prepared by the Frei test from an involved lymph node of a known case.[1, 2] Stained sections of primary skin lesions and involved lymph nodes from both man and monkeys show large numbers of intracellular and extracellular granulelike elementary bodies similar to those of psittacosis.[3] On the basis of similarity in the type of elementary body, a possible relation between the etiologic agent of cat-scratch fever and that of feline pneumonitis has been suggested.[4, 5] The infectious agent of the latter is antigenically related to the psittacosis-venereal lymphogranuloma viruses. This agent can be isolated readily, and passage is established in mice by intranasal instillation. A similar transfer of material from infected nodes of cat-scratch disease has not resulted in disease in mice. Efforts to isolate the infectious agent by the inoculation of other experimental animals have not proved successful; likewise, attempted cultivation by the use of conventional laboratory media and by tissue culture methods has been without success. Cats which transfer the agent to human subjects show no evidence of illness and have no reaction to the intradermal injection of the antigen.

Recently a preliminary report was published in the *Proceedings of the Society for Experimental Biology and Medicine* which concerns hemagglutination of rabbit erythrocytes by pus from cases of cat-scratch fever. This report by Dodd, Graber, and Anderson[6] is of considerable interest since it presents evidence of a viral type of hemag-

glutination and describes attempts to demonstrate specific hemagglutinin-inhibiting antibody in the serum of patients with this disease and in rabbits immunized by means of pus suspensions. Material from the lymph nodes was obtained from 10 persons with cat-scratch fever, the clinical diagnosis having been made on the basis of regional nonbacterial lymphadenitis and a history of cat scratch and verified in 8 of the 10 cases by positive skin tests to cat-scratch antigen. The pus, as aspirated, was diluted 1:5 in physiologic salt solution and 2 samples heated at 56° C. for 1 hour on consecutive days for the preparation of skin-test antigen. This lymph node material, either untreated or heated, was diluted serially in phosphate buffered saline through 1:512. One drop of each dilution was mixed with 1 drop of a 2 per cent suspension of washed rabbit red cells. The tubes were incubated in a water bath at 37° C. for 30 minutes followed by light centrifugation (1,500 r.p.m. for 30 seconds). Such preparations were observed for phenomenon of hemagglutination by gentle shaking of the tubes and notation of the appearance of clumping of red cells.

Similar tests were set up with the use of trypsinized erythrocytes prepared by treatment with 0.1 per cent trypsin for 30 minutes in a water bath at 37° C. and with tanned cells prepared by similar treatment with dilute tannic acid. Human sera tested for the possible detection of inhibition of hemagglutination included specimens obtained from some of the infected individuals from whom pus was taken from the lymph nodes, serum from a retested person with a known positive skin test to cat-scratch fever antigen, and for control, serum from an individual known to be suffering from an adenovirus infection. The rabbit sera were obtained before and after immunization of the animal with its own red cells previously treated with pus from the infected node of a patient with cat-scratch disease. Tests for the presence of a hemagglutinin-inhibiting antibody in the serum were based on standard procedures: the incubation of equal volumes of serum and a pus dilution, containing 4 hemagglutinating units, for 30 minutes in a water bath at 37° C. before testing for hemagglutination of red cells.

Rabbit erythrocytes were agglutinated by all 10 samples of pus from known or suspected cases of cat-scratch fever including the 2 patients in whom a positive skin test could not be evoked. Maximal agglutination was observed, however, only with samples of pus from patients with positive skin tests. Similar over-all results were obtained with the use of trypsinized and tanned red cells, but neither human cells nor sheep cells were agglutinated by the lymph node material. By way of comparison, similar agglutination tests were carried out using purulent material from the lymph nodes of 3 patients with lymphadenitis but with no clinical evidence or evidence from skin-tests of cat-scratch fever. No agglutination of red cells was detected. The presence of a hemagglutinin-inhibiting antibody was demonstrated consistently in the serum of rabbits immunized by material from lymph nodes of patients with cat-scratch fever. The serum of the patient suffering from adenovirus infection was entirely negative for this type of antibody. At the time of this report not all of the sera from patients with cat-scratch disease being tested showed this hemagglutinin-inhibiting antibody to the authors' satisfaction. These investigations are still in progress, together with virus elution studies as a means of verifying viral etiology.

In a summary discussion the authors state: "Lack of previous evidence of hemagglutination in cat scratch fever and the possibility that the procedures described may be useful in diagnosis of the disease prompted this preliminary report. Good evidence that the hemagglutinin is a virus has been obtained . . . and will be published."[6]

RUSSELL J. BLATTNER, M.D.

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Books

Tuberculosis Medical Research—National Tuberculosis Association, 1904-1955.
Virginia Cameron and Esmond R. Long, M.D., New York, 1959, National Tuberculosis Association, 325 pages. Price $5.00.

This book describes the many studies in tuberculosis sponsored and/or supported by the National Tuberculosis Association between 1904 and 1955. From these laboratory and clinical studies has come a better understanding of the problems of tuberculosis in all age groups. Most of the research supported by the National Tuberculosis Association has been directed toward broadening our knowledge of the bacteriologic, immunologic, and epidemiologic aspects of tuberculosis and related diseases.

The text has limited interest for most physicians since it is essentially an historical account of research supported by a single voluntary health organization.

ROBERT H. HIGH, M.D.

Fluid and Electrolyte Therapy: A Unified Approach.
Donald E. Pickering, M.D., and Delbert A. Fisher, M.D., Portland, 1959, The Medical Research Foundation of Oregon, 104 pages. Price $11.00.

The lack of comprehension concerning the theory and management of clinical fluid and electrolyte problems is a serious blot on our present methods of medical education. The results of these inadequacies are only too evident in the bewilderment of the student, intern, resident, and practicing physician alike when confronted with such problems. Any effort with the express purpose of providing solid cornerstones upon which to build reasonable concepts in this field deserves serious consideration.

In the foreword of the book it is stated that "the objectives of this book . . . are to present in concise form the fundamental principles regulating the volume and composition of body fluids and a simplified though rational procedure by which the physician can assay and correct disturbances in these fluids as encountered in various pathological states." With emphasis on "concise" and "simplified," the reviewer concedes that the authors have succeeded admirably.

The book is arranged in three general sections. Fluid and electrolyte homeostasis is discussed in terms of disorder of hydrogen ion concentration and volume and concentration of body fluids. The presentation is an amazingly good condensation of the present-day theories of the pathophysiology of these derangements. This section does, however, contain a serious error in the theory of antidiuretic hormone action that I trust will be corrected in future printings (i.e., that antidiuretic hormone *increases* water excretion).

The second section deals with general plans of treatment of maintenance, deficit, and contemporary fluid and electrolyte requirements.

The final section illustrates the authors' approach to specific problems such as diarrhea, vomiting, diabetic acidosis, salicylism, burns, and renal failure. Scattered throughout are numerous examples of their approach to the specific problems.

The appendix contains a list of the composition of the more commonly used electrolyte solutions and an example of a "flow" sheet that can be kept by the bed of any patient with a fluid or electrolyte problem.

The authors have devised a series of small (10 or 30 c.c.) vials of concentrated electrolyte solutions which may be added to readily available bottles of 5 per cent D/W. At first glance one might cringe at being forced to learn an entirely new set of pharmacologic concoctions. However, their versatility makes this an ingeniously simple but by no means the only method of therapy. A physician who understands the basic principles involved can continue to prepare the fluid electrolyte mixtures in a way with which he is already familiar and yet attain the same results.

In the attempt to be concise (the book is only 104 pages long) the authors have necessarily generalized occasionally. In addition some pertinent data, difficult to find, are alluded to but no specifics are given (e.g., the make up of a low

osmolar residue diet). Such defects are, however, relatively few in number and rarely concern important basic concepts. There is an ample bibliography available for anyone interested in pursuing a particular subject.

Accompanying the book is a circular calculator which allows rapid estimation of the probable fluid and electrolyte requirements of the patient, depending on the cause of the problem.

If the calculator, or indeed the book, is used solely as a crutch which enables one to quickly order and mix electrolyte "cocktails," then their publication will do more harm than good. If, however, the physician employs both of them to gain a better over-all picture of the problems that he faces and realizes full well that the book and calculator will neither diagnose the condition nor cure the patient, this two-in-one offer is a bargain at twice the price.

DANIEL S. FLEISHER, M.D.

Child Welfare: Principles and Methods. Dorothy Zietz, Ph.D., New York, 1959, John Wiley & Sons, Inc., 384 pages. Price $5.50.

As the author states in the introduction, "this book is addressed to the college classroom. It provides a backdrop for an examination of current services and traces the origins and antecedents of the various methods through which our communities attempt to meet the needs of children today." For the purpose for which it was intended, the book is worthy of merit. For the pediatrician, however, there is little of practical value to be gained from it. Dr. Zietz is to be complimented in making this material available to those who are, or will be, engaged in the ancillary services which are concerned with the various aspects of child welfare.

RICHARD W. OLMSTED, M.D.

News and notes

The Department of Pediatrics of the University of Florida College of Medicine has recently established training programs for (a) advanced work in immunology and infectious disease and (b) noncategorical training leading to research and teaching in pediatrics beginning July 1.

The first program, an interdisciplinary program jointly sponsored by the Departments of Medicine, Microbiology, and Pathology, is planned to foster competence in both basic and clinical aspects of infectious disease and immunology through a 2- to 3-year program. It is available to qualified individuals with a minimum of 1, preferably 2, years of straight internship or residency. Stipends begin at $6,000 per year.

The second program is designed to provide a period for intensive study, research, and teaching experience in the basic sciences related to major fields of pediatric research, as an initial phase in preparation for a career in full-time academic pediatrics. The basic fields currently available are (a) immunity and resistance mechanisms, (b) biophysical biochemistry, including polysaccharide and protein chemistry, and (c) mechanisms of embryogenesis, growth, and development. It is available to highly qualified individuals with a minimum of 1 year of straight pediatric internship or residency or the equivalent and plans for an academic career. Stipends start at $7,000 per annum. Specific plans for each program will be based on individual needs.

For further information contact Richard T. Smith, M.D., Department of Pediatrics, University of Florida College of Medicine, Gainesville, Fla.

A booklet, "I Went to the Hospital," has been written and illustrated for the preschool child anticipating a hospital stay by the Parents' Committee of the Children's Ward of Tompkins County Hospital, Ithaca, New York. For children of all ages and their parents, a 22 minute, 16 mm. color film, "A New World for Peter," shows what the child's hospitalization is like. The film was also prepared by the Parents' Group under the supervision of the Cornell University Photo Science Department.

"I Went to the Hospital" may be purchased for 25 cents per copy plus a 5 cents mailing charge. Bulk prices will be supplied on request. The film can be rented for $7.50 per day and prints can be purchased for $175.00. Correspondence should be directed to Post Office Box 23, Ithaca, N. Y.

For the coming year the **Long Beach Pediatric Society** has elected Dr. William Zantiny, president; Dr. Charles Latshaw, vice president; and Dr. Paul M. Kegan, secretary-treasurer.

The First Regional Pediatric Conference for the Middle East and the East Mediterranean was held in Cairo March 6 to 11 under the chairmanship of Prof. M. Diwany. Over 300 physicians, representing 17 countries, attended. Eight Americans, who were members of the United States Naval Research Unit, and a Canadian were present and participated in the program. The principal subjects discussed were rheumatic fever, poliomyelitis, nutritional problems, and tuberculosis.

A prominent part of the program was the social activities which were carried out with Oriental splendor and true Arabic hospitality.

The next meeting will be held in Ankara in the fall of 1961.

The American Board of Pediatrics, Inc., certified the following diplomates at New York, New York, on Feb. 26, 27, and 28, 1960.

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EDITOR'S COLUMN

Prevention of rheumatic fever recurrences

IN A RECENT paper, Lim and Wilson[1] have compared daily oral prophylactic penicillin with therapeutic doses of penicillin given for 10 days for every upper respiratory infection as a means of preventing rheumatic recurrences. Data on a total of 213 patients followed for a 6 year period are presented: 110 received continuous daily prophylactic penicillin and 103 intermittent penicillin therapy. The patients in the 2 groups, however, were not matched carefully in regard to number of rheumatic attacks, cardiac lesions, or age or interval since the last attack. Furthermore, some of the patients were switched from one group to another.

A larger number of recurrences were observed in the group on continuous daily prophylactic penicillin than in the group receiving intermittent penicillin therapy. Since the patients in the latter group were older and the interval since the last attack was longer, however, the comparison is not valid. The authors themselves state that if these factors are taken into consideration the rate of recurrence shows no significant difference between the 2 groups. In any study of rheumatic patients, unless cases are matched as closely as possible in every way, the significance of the results is open to question.

It is now well established that prophylaxis for the prevention of streptococcal infections reduces the incidence of rheumatic recurrences. At the present time 3 prophylactic regimens are commonly used: monthly intramuscular injections of 1,200,000 units of benzathine penicillin G, oral penicillin, 200,000 units twice daily, or sulfadiazine, 0.5 to 1 Gm. once a day.[2] The first regimen is foolproof and the most effective.[3] The 2 oral regimens are somewhat less reliable because they depend on the cooperation of the patient.

In comparison with a regimen in which penicillin is given whenever signs of an upper respiratory infection develop, the standard prophylactic measures recommended by the American Heart Association have distinct advantages. Rheumatic children, who often have had long bouts of illness, tend not to report minor symptoms. Furthermore, rheumatic recurrences frequently follow subclinical streptococcal infections which would not be treated.[4] The majority of upper respiratory infections are of viral rather than of streptococcal origin.[5] Therapeutic doses of penicillin, therefore, would be given unnecessarily at frequent intervals. The generally accepted methods for the prevention of recurrences of rheumatic fever, therefore, are preferable to a regimen of intermittent therapy given only when signs of an upper respiratory infection are detected.

ANN G. KUTTNER, M.D.

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The superior child: selective precocity

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As in music and mathematics, precocity is not infrequent among the great masters of chess. Samuel Reshevsky learned the game at 3½ years of age and at the age of 8 defended himself ably against some of America's best players. José Capablanca, who wrested the world championship from Emanuel Lasker, learned to play at 4 years of age. Paul Morphy, one of the great chess masters of all times, began his career at 12 years of age and quickly overcame all opponents in his native New Orleans.

Chess playing is unique among the great skills in that it can be acquired without book learning. Reuben Fine, an author of several books on chess, states that he never read a book on the subject until he became a master. Emanuel Lasker, who retained the world championship for 27 years, rarely looked at a book on chess, although he read widely in other fields, particularly mathematics and philosophy.

Precocity in chess, as in music and mathematics, requires a high order of general intelligence, opportunity to see the game played, strong motivation, and a combination of mental qualities especially suited to the subject at hand. Unlike music, chess does not "run in families." It is notable that in chess, as in musical composition, no woman has ever achieved a place of high eminence.

The unique feature of young Fischer's career is the speed with which he has risen to the top in the chess world. Taught by his 10-year-old sister, he began to play chess at 6 years of age, but it was not until he was 13 that he began to take the game seriously. Since then he has made chess history. None of the precocious chess players of the past reached the heights attained by Fischer at so early an age. At 15 he won the title of International Grand Master, the highest position open to a chess player next to World Champion. At 16 years of age he is regarded by many as one of the 20 best players in the world and as a probable future contender for the world championship. Already his plays show the quality of greatness.

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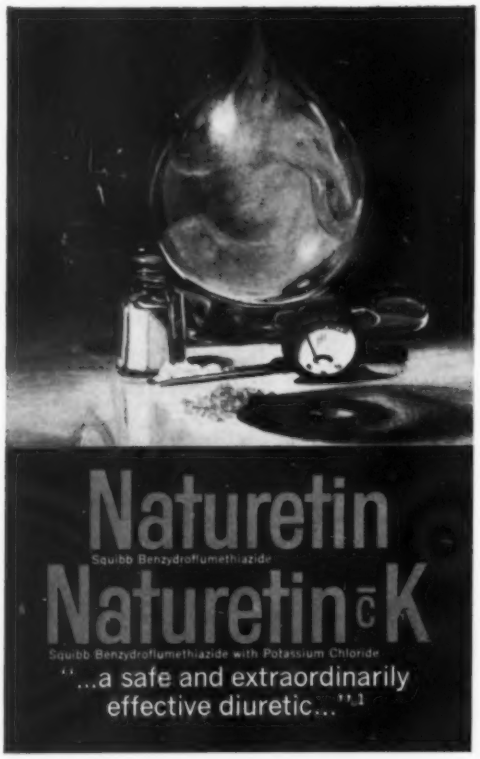

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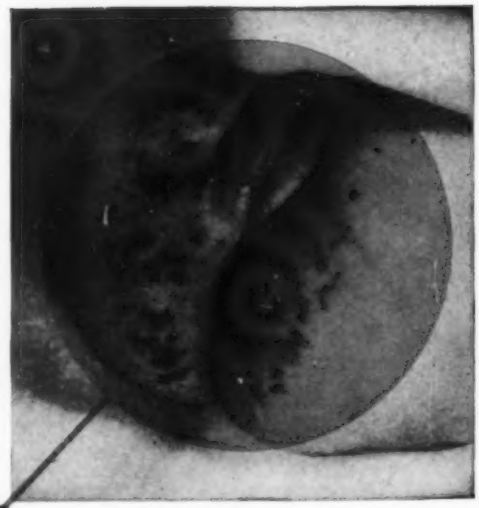

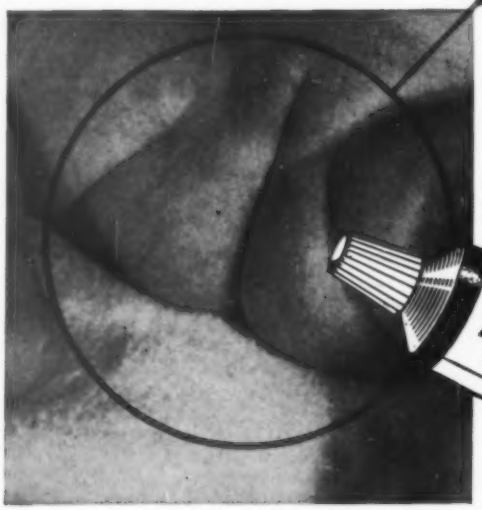

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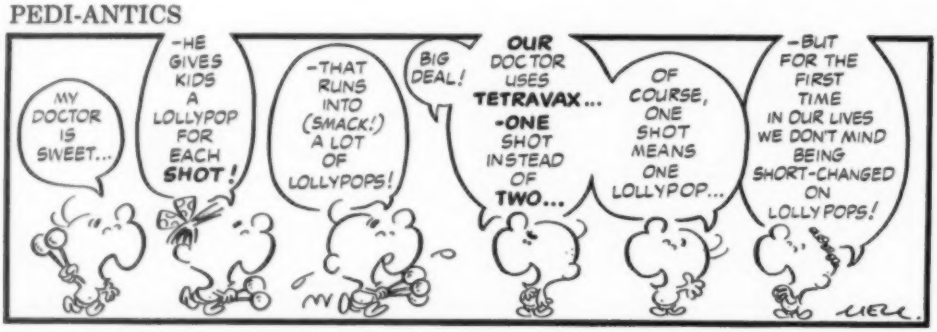
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Aldrich's syndrome.
Antonio M. Rivera, Captain, USAF (MC), and Frederick C. Biehusen, Major (MC) USA, San Francisco, Calif.

The present state of knowledge on the celiac syndrome.
A. C. Frazer, M.D., Ph.D., D.Sc., F.R.C.P., Birmingham, England.

Comparison of ocular reactions with the use of silver nitrate and erythromycin ointment in ophthalmia neonatorum prophylaxis.
Joseph R. Christian, M.D., Chicago, Ill.

Diseases of nutritional deficiency of children in South India.
C. Gopalan, M.D. (Madras), Ph.D. (London), Hyderabad, India.

Progeria, a pathologic study.
Mamdooh Gabr, M.D., Nemat Hashem, M.D., M. Hashem, M.D., A. Fahmi, Ph.D., and M. Safouh, M.D., Cairo, Egypt, U.A.R.

Overwhelming infection in children following splenectomy.
Russell V. Lucas, Jr., and William Krivit, Minneapolis, Minn.

Sturge-Weber syndrome: nonsurgical management.
Arthur G. Smith, M.D., and Allan B. Ramsay, M.D., Hazard, Ky.

The effects of intermittent doses of adrenocortical steroids on the statural growth of nephrotic children.
Daniel S. Fleisher, M.D., Wallace W. McCrory, M.D., and Milton Rapoport, M.D., Philadelphia, Pa.

Congenital tuberculosis.
Sarah F. Davis, Sara C. Finley, and W. Kendrick Hare, Birmingham, Ala.

A report of 16 spinal cord tumors in children; the importance of spinal rigidity as an early sign of disease.
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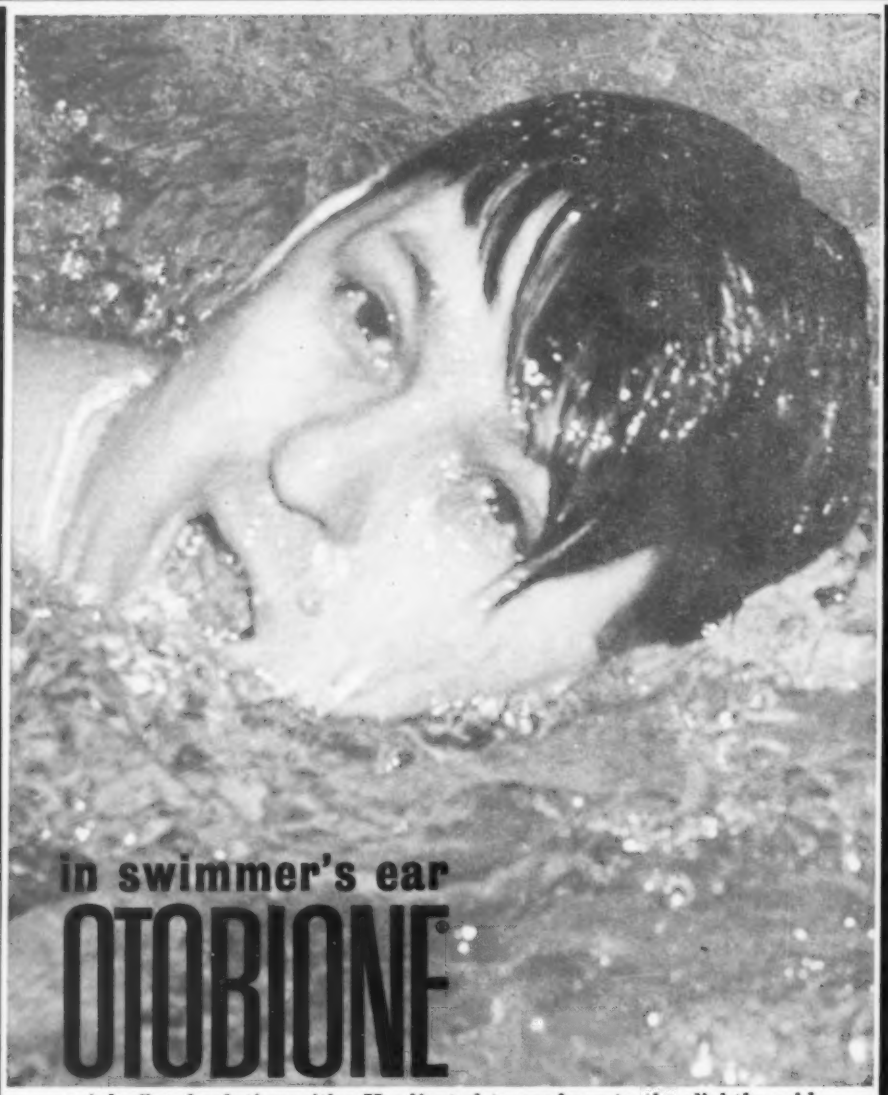

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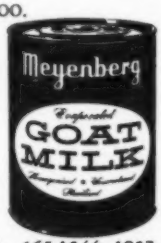
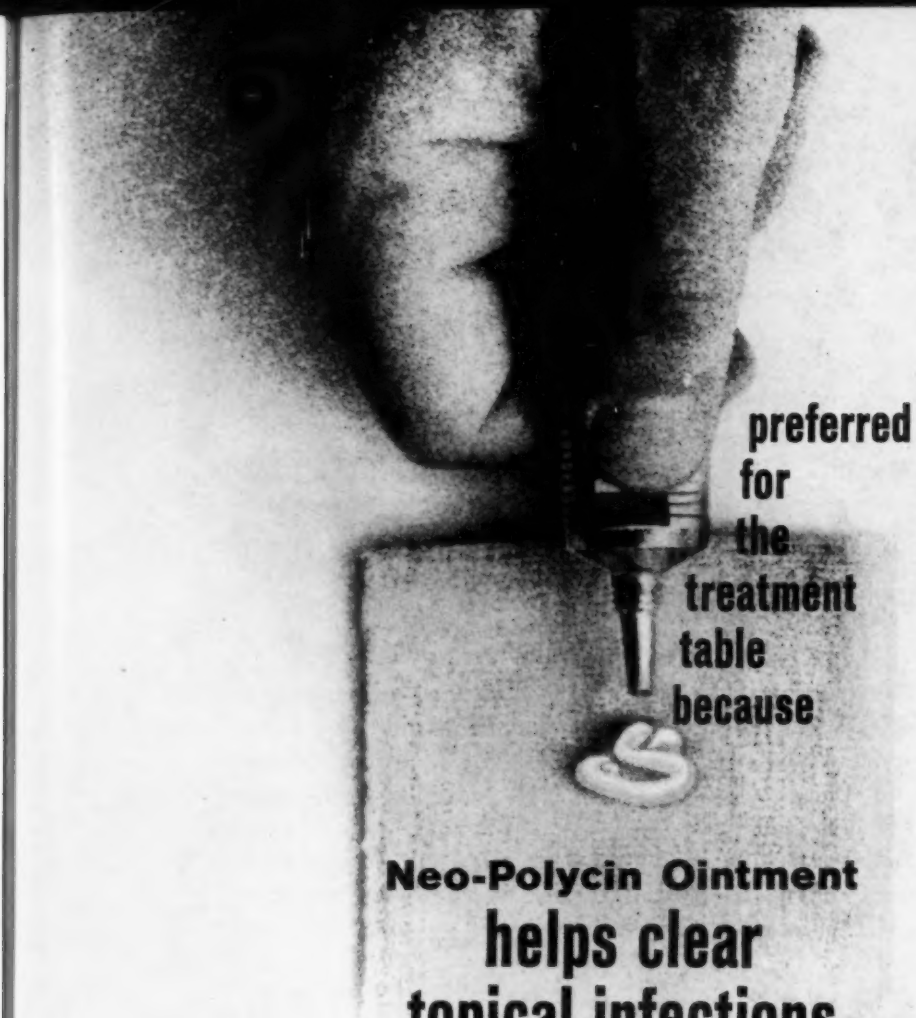


*Fries, J. H.: Milk Allergy—Diagnostic Aspects and the Role of Milk Substitutes, J.A.M.A., *165*:1544, 1957.



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References: 1. Alonso, M.: Bol. As. Med. Puerto Rico 50:105, 1958. 2. Benton, C. D., Jr.: South. M. J. 48:546, 1955. 3. Peele, J. C.: Laryngoscope 63:488, 1953. 4. Leopold, I. H.: J. M. Soc. N. Jersey, 53:213, 1956.

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1. Susca, L. A.: Treatment of diaper rash, New York J. Med., to be published. 2. Levine, A. J., et al.: Influence of amino acid therapy in chronic idiopathic pruritus ani, Gastroenterology 35:409, 1958. 3. Review: Requirements for sulfur amino acids, Nutrition Rev. 17:74, 1959. 4. Christian, J. R., and Gonzalez, F. A.: The topical treatment of acute and chronic diaper rash with an amino acid cream, Clin. Med., to be published. 5. Editorial: Diaper rash, J.A.M.A. 165:254, 1957.

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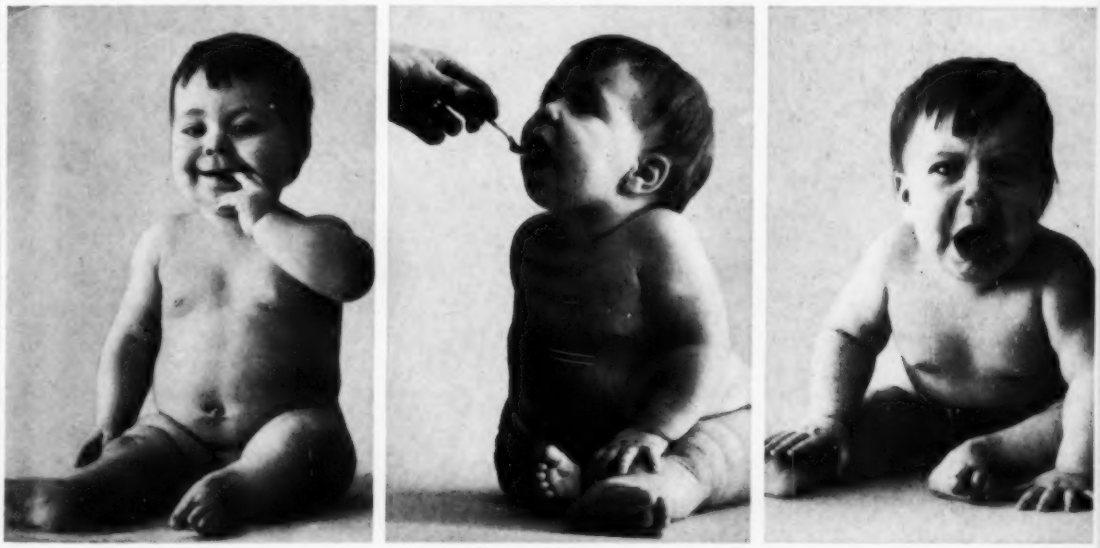

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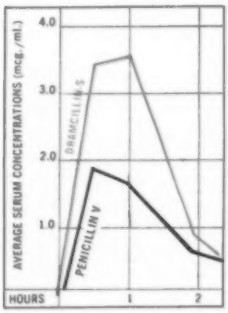

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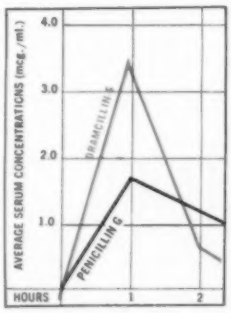

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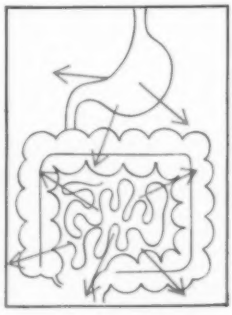

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References: 1. Wright, W.: Cited by Morigi et al.[3] 2. Pindell, M. H.; Tisch, D. E.; Hoekstra, J. B., and Reifenstein, J. C.: Antibiotics Annual, 1959-1960, p. 119. 3. Morigi, E. M. E.; Wheatley, W. B., and Albright, H.: Antibiotics Annual 1959-1960, p. 127.

**with regard to immediate blood levels*

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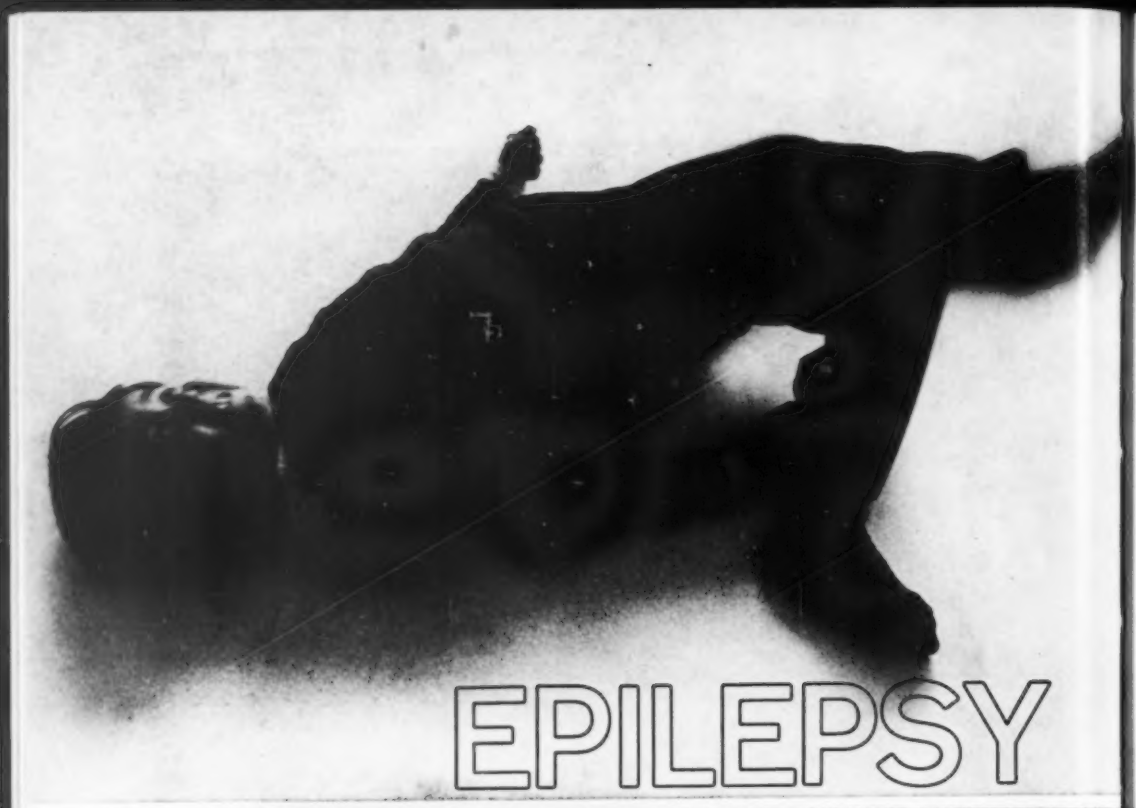

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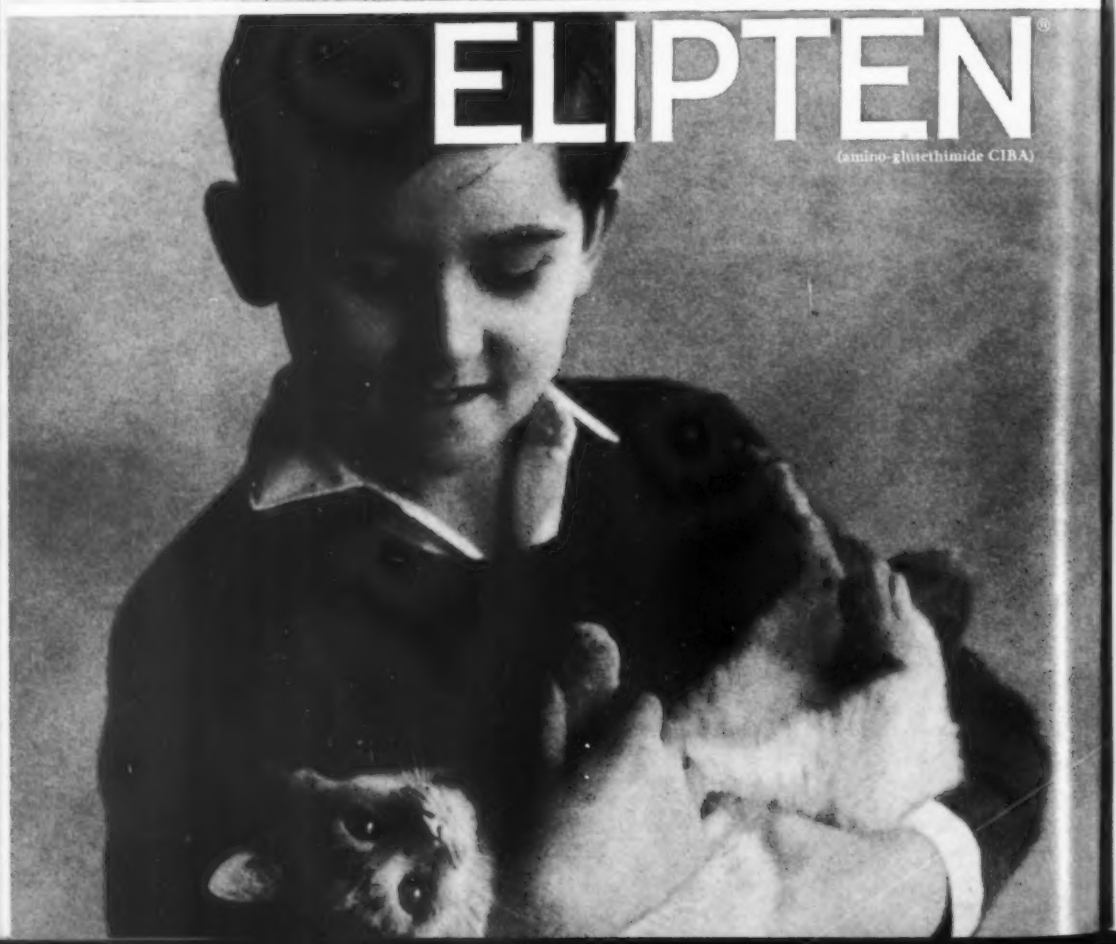

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By obviating or reducing the need for barbiturates, Elipten improves alertness and learning ability in children. It has little or no toxic effect on liver, kidney, or blood.

Clinical Reports

Forster[1] states: "Elipten . . . has a definite role in improving the therapy, particularly of petit mal epilepsy." He notes further that Elipten ". . . oftentimes will turn the tide when added to partially successful medication." Meyer[2] observes: ". . . this drug is useful in generalized and localized convulsions as well as in status epilepticus. In addition, it is useful in the control of petit mal epilepsy and is of particular benefit in those cases where petit mal and generalized convulsions are combined. We have found it less useful in temporal lobe seizures." Lambros[3] notes complete control or marked improvement in 27 of 35 patients treated with Elipten (13 were gradually switched to Elipten alone; 14 were given other anticonvulsants adjunctively). Niswander and Karacan[4] report that in 38 hospitalized psychotic epileptic patients given Elipten, grand mal seizures were reduced 25 to 35 per cent. Carter[5] recommends concomitant use of Elipten and diphenylhydantoin sodium ". . . to enhance effectiveness and reduce the dosage of both drugs."

While most investigators report that a transient skin rash occurs in some patients, especially when initial dosage is high, Sheehan[6] states: "On reduction of the dose, this rash quickly disappears and does not recur when the dose is gradually stepped up to its original level." Forster[1] also notes that ". . . this [the rash] is not a serious complication and does not rule out Elipten therapy."

Complete information on Elipten is available on request.

SUPPLIED: *Tablets,* 250 mg. (white, scored); bottles of 100.

References: **1.** Forster, F. M.: Wisconsin M. J. *58*:375 (July) 1959. **2.** Meyer, J. S.: M. Times *87*:743 (June) 1959. **3.** Lambros, V. S.: Dis. Nerv. System *19*:349 (Aug.) 1958. **4.** Niswander, G. D., and Karacan, I.: Am. J. Psychiat. *116*:260 (Sept.) 1959. **5.** Carter, C. H.: Dis. Nerv. System *21*:50 (Jan.) 1960. **6.** Sheehan, S.: Irish J. M. Sc. *390*:261 (June) 1958.

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sulfa therapy suited
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Employs the N¹ acetyl form of KYNEX to impart high palatability yet retain single-daily-dose effectiveness and rapid, high sustained action against sulfa-susceptible infections. **Dosage:** first day, 1 tsp. (250 mg.) for each 20 lbs.; thereafter, ½ tsp. daily for each 20 lbs. For 80 lbs., use adult dosage of 4 tsp. (1.0 Gm.) initially; and 2 tsp. (0.5 Gm.) thereafter. Taken once a day—preferably after a meal. **Supplied:** Each tsp. (5 cc.) contains 250 mg. sulfamethoxypyridazine activity. Bottles of 4 and 16 fl. oz.

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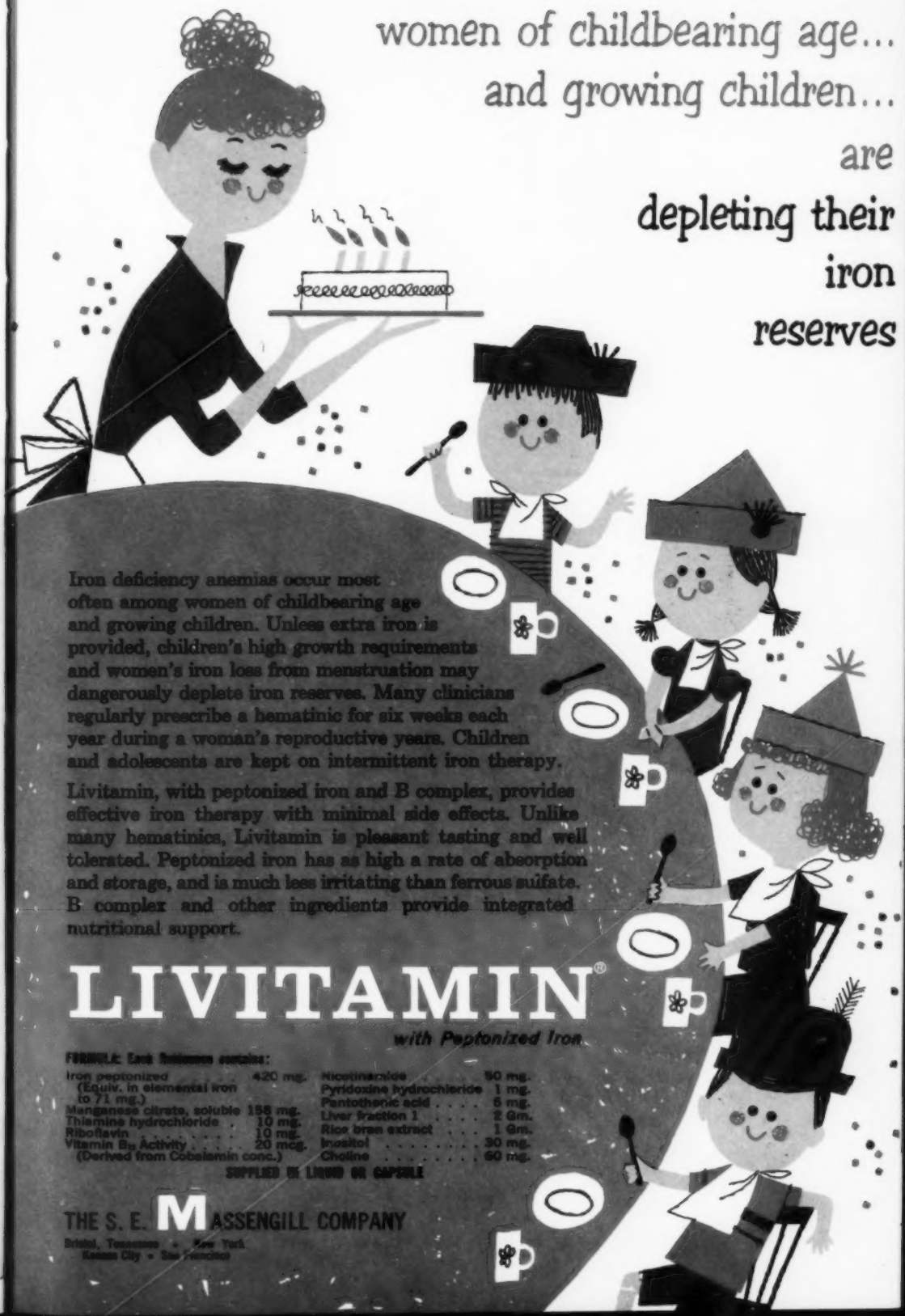
women of childbearing age...
and growing children...
are
depleting their
iron
reserves



Iron deficiency anemias occur most often among women of childbearing age and growing children. Unless extra iron is provided, children's high growth requirements and women's iron loss from menstruation may dangerously deplete iron reserves. Many clinicians regularly prescribe a hematinic for six weeks each year during a woman's reproductive years. Children and adolescents are kept on intermittent iron therapy.

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with Peptonized Iron

FORMULA: Each Teaspoonful contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.	Nicotinamide	50 mg.
Manganese citrate, soluble	155 mg.	Pyridoxine hydrochloride	1 mg.
Thiamine hydrochloride	10 mg.	Pantothenic acid	5 mg.
Riboflavin	10 mg.	Liver fraction 1	2 Gm.
Vitamin B_{12} Activity (Derived from Cobalamin conc.)	20 mcg.	Rice bran extract	1 Gm.
		Inositol	30 mg.
		Choline	60 mg.

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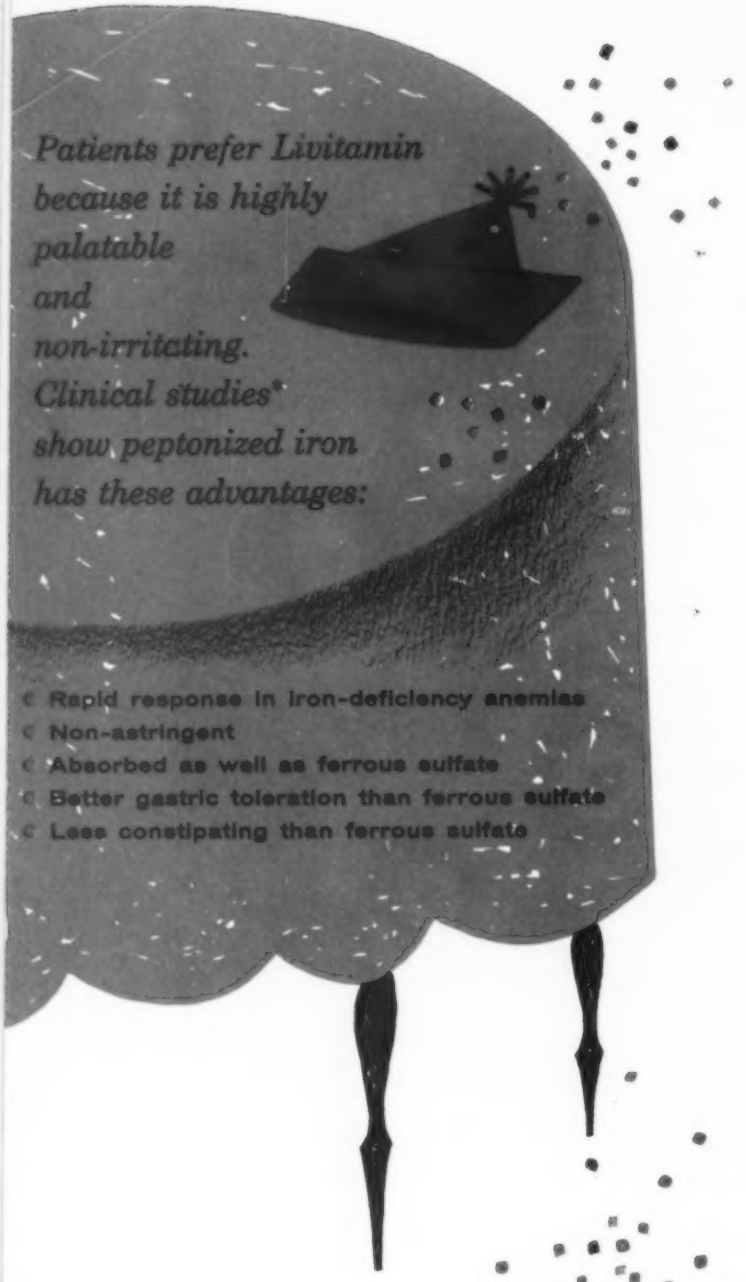

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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

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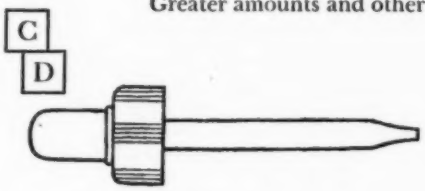

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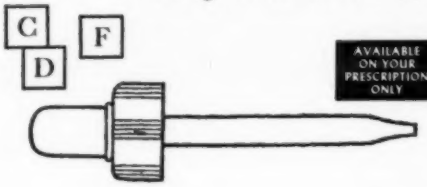

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REFERENCES: 1.) Council on Foods and Nutrition: Vitamin Preparations As Dietary Supplements And As Therapeutic Agents. J.A.M.A. 169:110 (Jan. 3) 1959. 2.) May, C. D.: Editorial. Pediatrics. 23:833 (May) 1959. 3.) Sebrell, Jr., W. H.: Vitamins In Medical Practice. Seminar Report, 3:2 (Fall) 1958. 4.) Smith, D. W., Blizzard, R. M. and Harrison, H. E.: Idiopathic Hypercalcemia. Pediatrics, 24:268, (August) 1959. 5.) Council on Dental Therapeutics: Prescribing Supplements Of Dietary Fluorides. J.Am. Dental Assoc. 56:589-591 (April) 1958.

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SAMPLES AND LITERATURE—write Medical Department

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1. Frech, H. C., and Lanier, L. R., Jr.: Am. J. Obst. & Gynec. 74:1148, 1957. 2. Way, W. G., et al.: Virginia M. Month. 85:291, 1958. 3. Hellman, L. D.: To be published.

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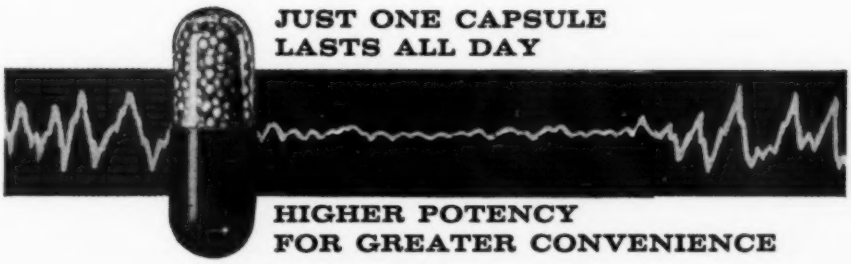

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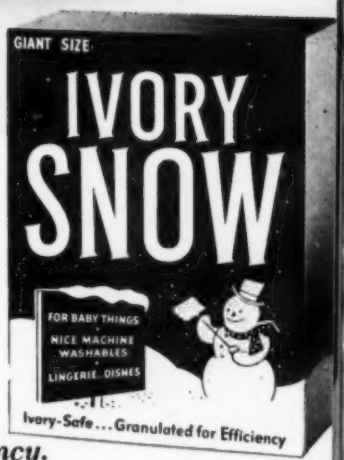

1. Because it's as safe a soap as a mother can use . . . leaves diapers and baby clothes soft, gentle-clean . . . and completely free from irritating deposits that can chafe tender skin!

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rapid remission of bacterial diarrhea

For superior adsorbent action, POLYMAGMA contains Claysorb which is five times more adsorbent than kaolin. The two antibiotics in POLYMAGMA—polymyxin and dihydrosteptomycin—provide synergistic bactericidal action against common enteric pathogens to help restore normal intestinal function.

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†Bartell, P., Pierzchala, W., and Tint, H.: J. Am. Pharm. A. (Sc. Ed.) *49*:1 (Jan.) 1960.

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NEOMYCIN—rapidly bactericidal against most intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

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"In recent years the serious pathologic effects of an overload of iron on structure and function of organs have received much attention."

Schulman, I.: Pediatrics 18:299, 1956.

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Von Oettingen, W. F.: Poisoning, ed. 2, Philadelphia, Saunders, 1958, p. 391.

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Also available: CHĒL-IRON PLUS Tablets—chelated iron plus B_{12}, folic acid, other B vitamins, and C.

1. Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, 1958. 2. A.M.A. Council on Drugs: J.A.M.A. 171:891, 1959. 3. A.M.A. Committee on Toxicology: Accidental Iron Poisoning in Children, J.A.M.A. 170:676, 1959.

KINNEY & COMPANY, INC.
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*U. S. Pat. 2,575,611

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"Functional vomiting should be carefully distinguished from organic vomiting. Grave consequences may follow if evidences of organic derangement, such as tumors or acute conditions requiring surgical therapy, are masked by treatment designed to control vomiting alone."

Bradley, J. E.: Mod. Med. 20:71, No. 20, 1952.

"The phenothiazine tranquilizer drugs should not be used indiscriminately for symptomatic treatment without due appreciation of the alarming and potentially serious side effects which may follow relatively small doses, especially in childhood."

Shaw, E. B., et al.: Pediatrics 23:485, 1959.

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1. Bradley, J. E., et al.: J. Pediat. 38:41, 1951. 2. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

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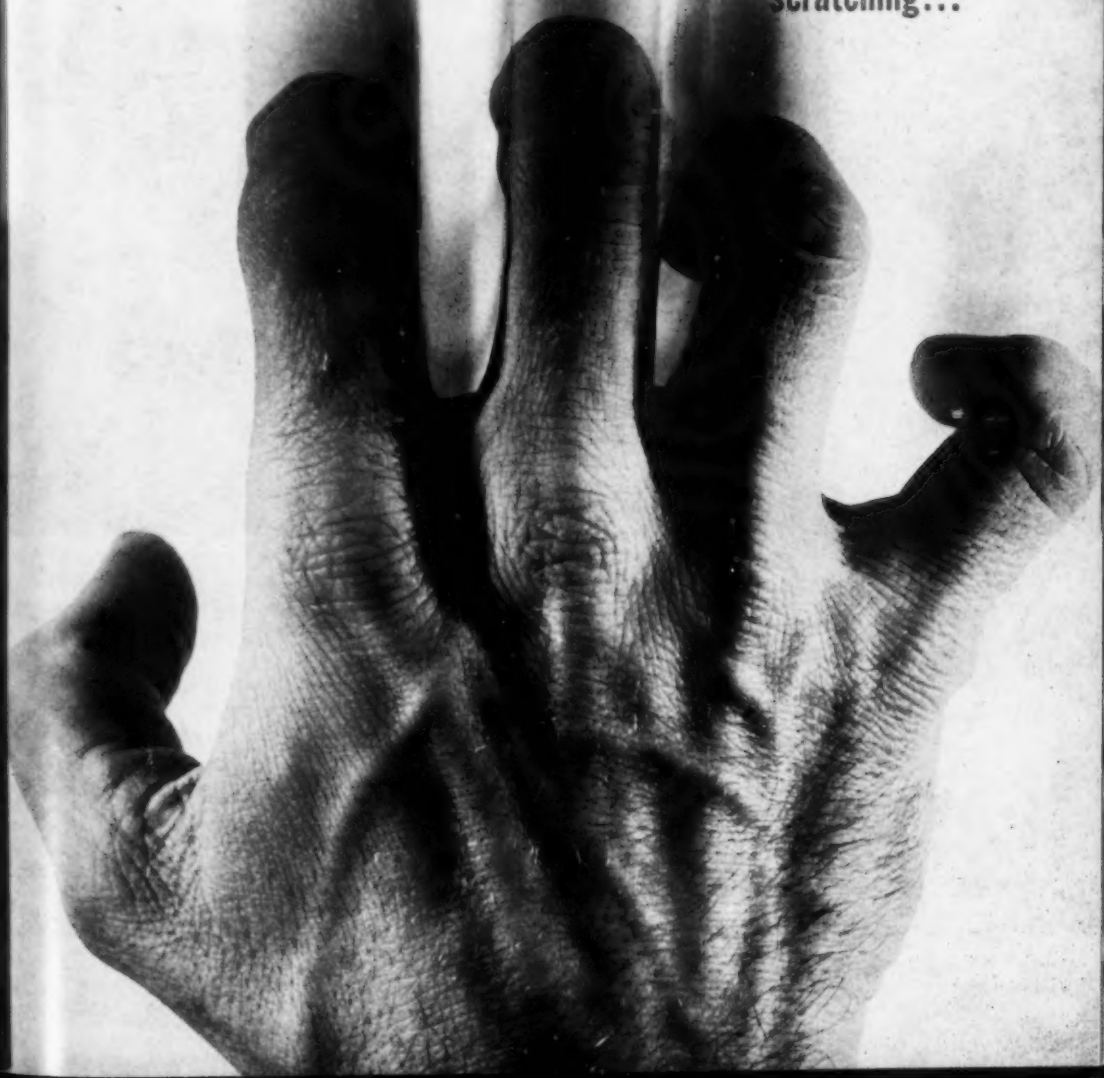

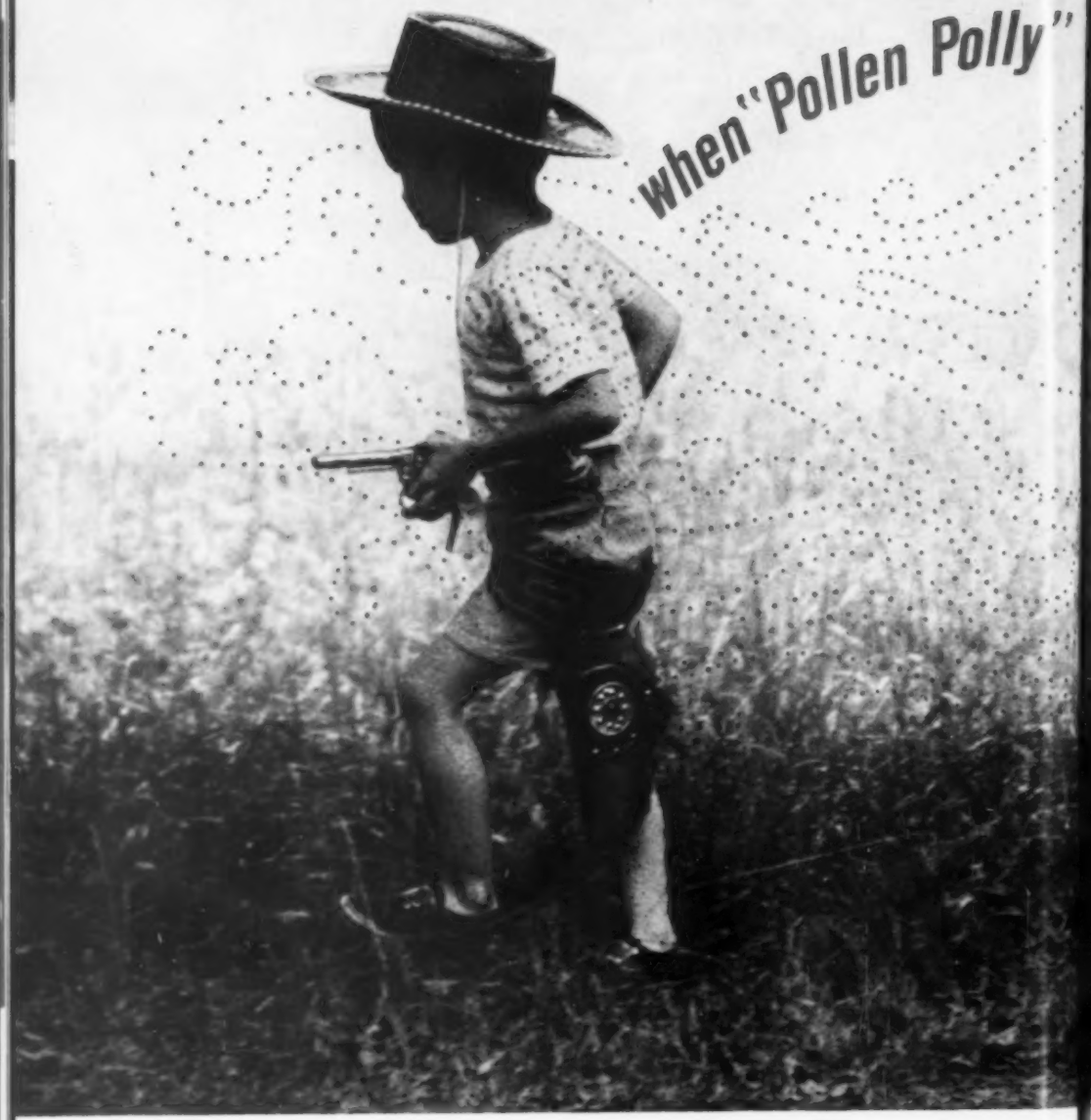

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more complete than antihistamines alone... more thorough than nose drops or sprays

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References: 1. Fabricant, N. D.: E.E.N.T. Monthly *37*:460 (July) 1958. 2. Lhotka, F. M.: Illinois M. J. *112*:259 (Dec.) 1957. 3. Farmer, D. F.: Clin. Med. *5*:1183 (Sept.) 1958. 4. Fuchs, M.; Bodi, T.; Mallen, S. R.; Hernando, L., and Moyer, J. H.: Antibiotic Med. & Clin. Ther. *7*:37 (Jan.) 1960. 5. Halpern, S. R., and Rabinowitz, H.: Ann. Allergy *18*:36 (Jan.) 1960.

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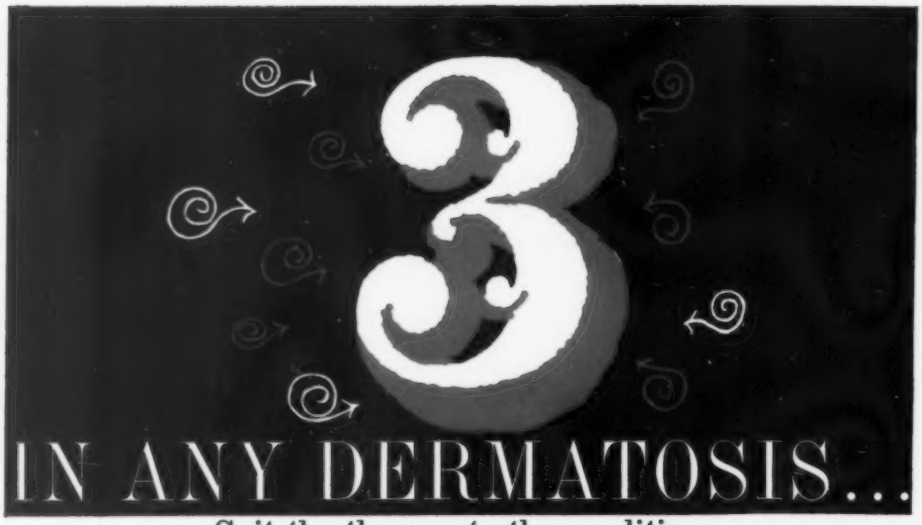

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1. Jones, E. H.: Eye, Ear, Nose & Throat Month. *38*:460, 1959. 2. Lockwood, J. H.: Bull. A. Mil. Dermatologists *4*:2, 1955.

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Vitamin A 1.5 mg...(5,000 U.S.P. units) (Synthetic)	3.3 MDR	1.7 MDR
Vitamin D 25 mcg...(1,000 U.S.P. units)	2.5 MDR	2.5 MDR
Vitamin C 50 mg.	5.0 MDR	2.5 MDR

Supplied: 15 cc., 50 cc.
both in amber bottles with separate, plastic calibrated dropper (0.3 and 0.6 cc.)

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Each 0.6 cc. contains:	Each 0.6 cc. supplies the following Minimum Daily Requirements (MDR): Infants	Children
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Vitamin D 25 mcg...(1,000 U.S.P. units)	2.5 MDR	2.5 MDR
Vitamin C 75 mg.	7 MDR	3.5 MDR
Pyridoxine HCl (B_6) 1 mg.	(Minimum Daily Requirement not established)	
Riboflavin (B_2) 1 mg.	2 MDR	2 MDR
Thiamine HCl (B_1) 1 mg.	4 MDR	1.5 MDR
Cyanocobalamin (B_{12}) 3 mcg.	(Minimum Daily Requirement not established)	
Nicotinamide 10 mg.	2 MDR	1.3 MDR

Supplied: 15 cc., 50 cc.
both in amber bottles with separate, plastic calibrated dropper (0.3 and 0.6 cc.)

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Each 5 cc. (1 teaspoonful) contains:	Each 5 cc. supplies the following Minimum Daily Requirements (MDR): Infants	Children
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Vitamin D 25 mcg...(1,000 U.S.P. units)	2.5 MDR	2.5 MDR
Vitamin C 50 mg.	5 MDR	2.5 MDR
Pyridoxine HCl (B_6) 1.0 mg.	(Minimum Daily Requirement not established)	
Riboflavin (B_2) 1.5 mg.	2.5 MDR	1.7 MDR
Thiamine HCl (B_1) 1.5 mg.	6 MDR	2 to 3 MDR
Cyanocobalamin (B_{12}) 5 mcg.	(Minimum Daily Requirement not established)	
Nicotinamide 10 mg.	2 MDR	1.3 MDR

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"no intolerance to molybdenized iron"[1]
... in a study of anemic premature infants — but 20% were intolerant to other iron salts. Mol-Iron is not just an ordinary iron salt — It is a specially processed co-precipitated complex of ferrous and molybdenum salts. Molybdenum is reported to protect the ferrous iron from oxidation to the more irritant ferric form... hence, the unmatched tolerance of Mol-Iron.[2]*

Mol-Iron® liquid & drops...
(Molybdenized-Ferrous Complex)

for therapy and prophylaxis of iron deficiency in children and infants

Mol-Iron Liquid: 12 fl. oz. bottles, each tspfl. contains 195 mg. ferrous sulfate and 3 mg. molybdenum oxide. **Mol-Iron Drops:** 15 cc. and 50 cc. bottles with dropper, each cc. contains 125 mg. ferrous sulfate and 2 mg. molybdenum oxide.

1. Tuttle, A. H., and Etteldorf, J. N.: J. Ped. 41:170, 1952. 2. Kelly, H. T.: Pennsylvania M. J. 51:999, 1948.

*COMPLETE BIBLIOGRAPHY AVAILABLE ON REQUEST.

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Schering

allergic to animals? in any case, for allergic symptoms, the most widely used antihistamine is CHLOR-TRIMETON.

S-479

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a low cost practical technic for the small INFANT-FORMULA ROOM

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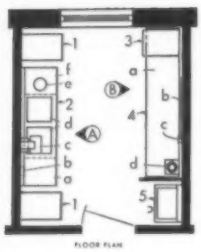
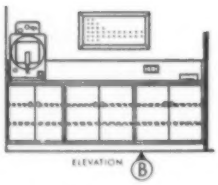
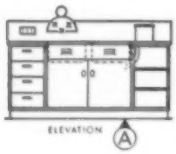


FLOOR PLAN



ELEVATION (B)



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Permits a Modern Formula Room in the minimum area.

With the model 832 as the basic unit, Amsco has developed special techniques and complete equipment suitable to Formula Room planning for the small nursery. Layout and equipment are fully in harmony with the most advanced standards of infant formula processing and work simplification . . . yet the space requirements and all-inclusive costs are extremely modest.

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Findings in 90 infants with manifestations of colic[1, 2] showed 11% with a butterfat intolerance and 31% with a carbohydrate intolerance. Varamel, a completely flexible formula, offers these safeguards: ■ butterfat is entirely replaced with well-tolerated vegetable oils; ■ double homogenization reduces fat globule size; ■ no carbohydrate has been added to Varamel. The doctor controls the amounts of water and carbohydrate in a Varamel formula, confident that a happy, well-adjusted baby will be the result. The Baker Laboratories, Inc., Cleveland 3, Ohio.

1. Breslow, Lawrence: Clinical Approach to Infantile Colic. J. Ped. 50:196-206, 1957*
2. Breslow, Lawrence: Analysis of Etiology of Colic in Infants (excerpts from a Panel Discussion, American Academy of Pediatrics). Pediatrics 18:838-9, 1956*

*Available upon request.

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- No sympathomimetic stimulation
- No barbiturate depression
- No suppression of adrenal function

Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydroalcoholic vehicle (alcohol 20%).

For acute attacks: When theophylline in any form has *not* been administered orally or parenterally within the preceding 6 hours, or per rectum within 12 hours—dose is 0.5 cc. per lb. body weight. Do not repeat in less than 6 hours, with no more than two such doses in a 24 hour period.

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1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.
2. Bradwell, E. K.: Acta med. scand. 146:123, 1953.
3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.

REFER TO PDR PAGE 812

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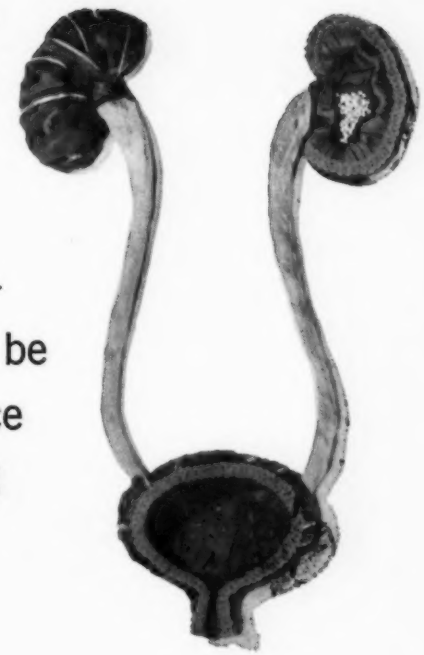
Just a "simple" case of cystitis may be the precursor of pyelonephritis[1]— or may actually be the first evidence of a pre-existing pyelonephritic process.[2]



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to ensure rapid control of infection throughout the urogenital system

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REFERENCES: 1 Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

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A Superior Oral Penicillin for Children

SUPPLIED: *Cherry flavor* —**300,000 units per 5-cc. tsp., bottles of 2 fl. oz.**
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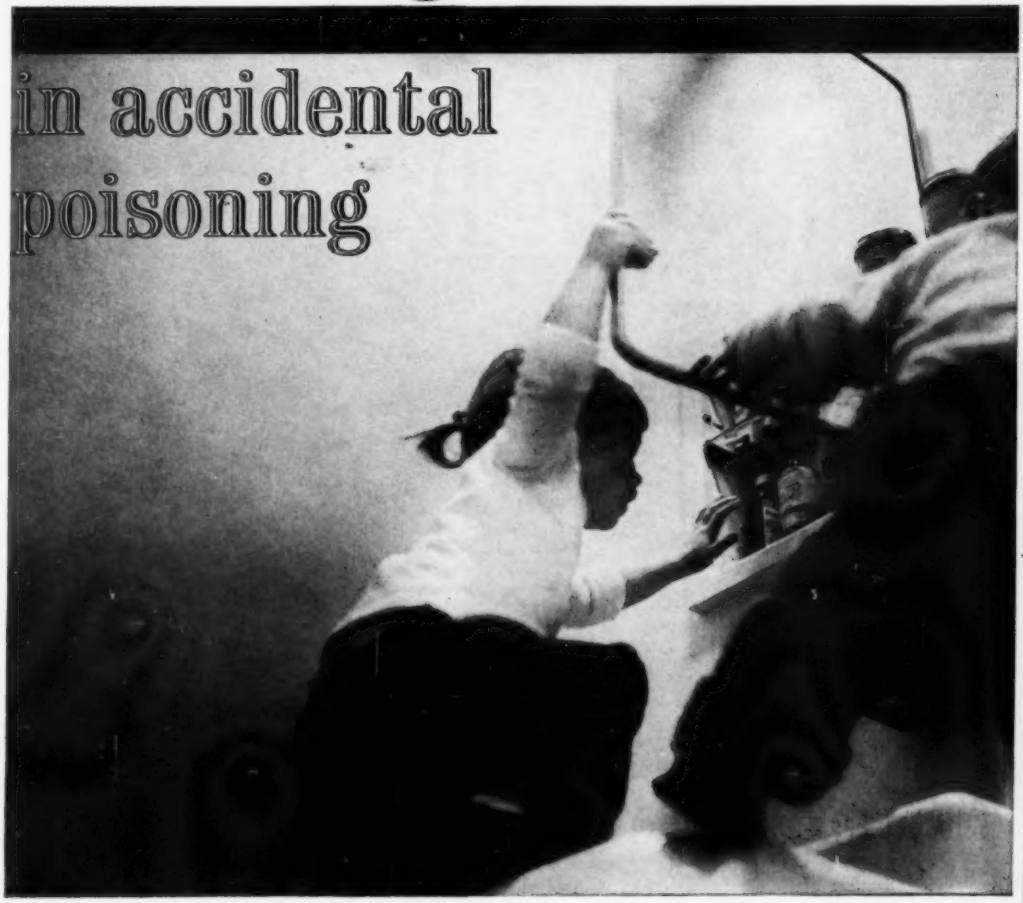

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Promptly kills parasites and eggs / simple to use / esthetically pleasing / no stinging, burning or unpleasant odor / nonstaining.

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REFERENCES: 1. Gardner, J.: J. Pediat. 52:448 (Apr.) 1958. 2. Halpern, L. K., et al.: A.M.A. Arch. Dermat. 62:648 (Nov.) 1950. 3. Cannon, A. B., and McRae, M. E.: J.A.M.A. 138:557 (Oct.) 1948.

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IN ALLERGY	"All [asthmatic] patients reported greater calmness and were able to rest and sleep better ... they needed much less antiasthmatic medication and led a more normal life.... In chronic urticaria, however, hydroxyzine was effective as the sole medicament." Santos, I. M., and Unger, L.: Presented at 14th Annual Congress, American College of Allergists, Atlantic City, New Jersey, April 23-25, 1958.	Nathan, L. A., and Andelman, M. B.: Illinois M. J. 112:171 (Oct.) 1957. Schuller, E.: Gaz. des Hôpitaux 129:391 (Apr. 10) 1957.
IN FEAR-PROVOKING SITUATIONS	"Atarax also may be used advantageously to reduce anxiety in children who become distressed when faced with unpleasant fear-provoking situations such as diagnostic tests in the hospital ... and minor surgical operations." Ayd, F. J., Jr.: California Med. 87:75 (Aug.) 1957.	Maryssael, L.: Bruxelles-méd. 38:141 (Jan. 26) 1958. Schicker, H.: Der Anaesthesist 6:371 (Dec. 6) 1957.

Dosage: 3-6 years, one 10 mg. tablet or one tsp. syrup t.i.d.; over 6 years, two 10 mg. tablets or two tsp. syrup t.i.d.

Supplied: Tiny 10 mg. tablets, bottles of 100. Syrup (10 mg. per tsp.), pint bottles. Prescription only.

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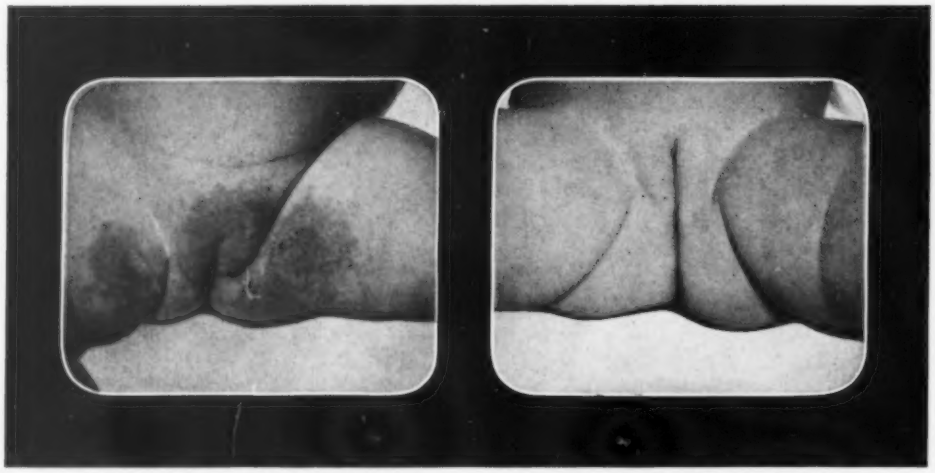

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In a well controlled institutional study,[1] the investigators report that Enfamil produced:

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1. Brown, G. W.; Tuholski, J. M.; Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Evaluation of Prepared Milks for Infant Nutrition; Use of the Latin Square Technique, J. Pediat. 56:391 (Mar.) 1960.

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*Gordon, H. H., and Ganzon, A. F.: J. Pediat. 54:503 (April) 1959.

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THE POTENTIATED DECONGESTANT

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safe and effective for patients of all ages suffering from upper respiratory tract congestion

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	TABLETS	SYRUP (5 cc. tsp.)	
Adults and older children	1	2	three times daily
Children 4 months to 6 years of age	½	1	
Infants through 3 months	–	½	

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ECZEMA

and other major symptoms of cow's milk allergy

Kane[1] fed Sobee to 76 eczematous infants ranging in age from 1 week to 9 months. Marked improvement occurred in 75 of the 76 infants.

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1. Kane, S.: Am. Pract. & Digest Treat. 8: 65 (Jan.) 1957.

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orange juice
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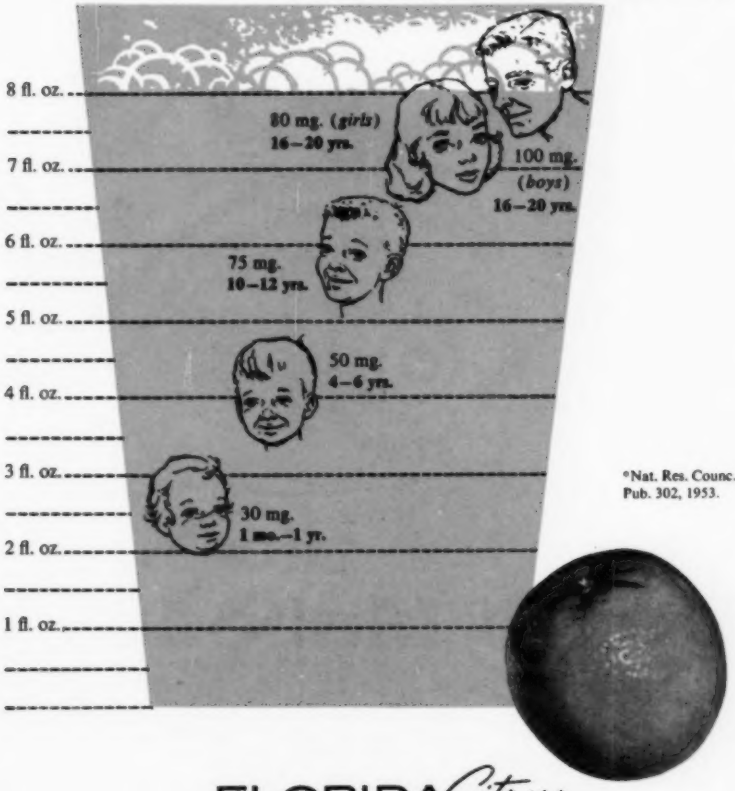

*Nat. Res. Counc., Pub. 302, 1953.

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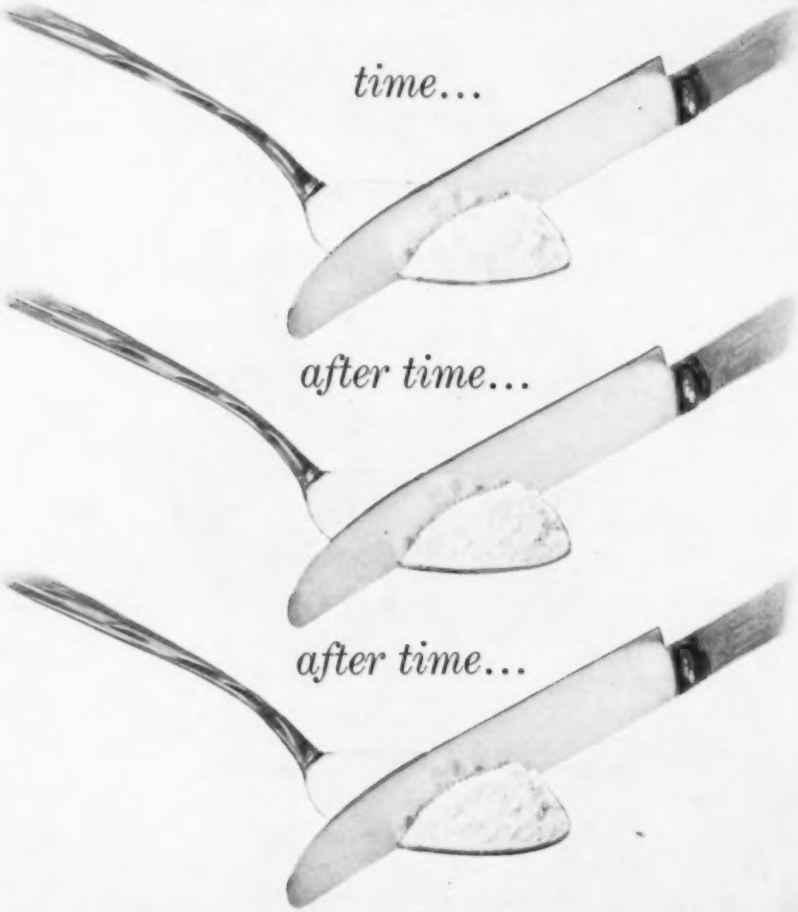

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Since heat and sweating intensify prickly heat,[1] removal to a cool environment and reduction of sweating is an important first step in relieving the patient.

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References: 1. Pillsbury, D. M., Shelley, W. B., and Kligman, A. M.: Dermatology. Philadelphia, W. B. Saunders Company, 1956. 2. Waisman, M.: in Current Therapy, 1960. Ed. by Conn; Phila., W. B. Saunders Co.

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Aveeno-Bar offers the specific skin-calmative properties of Aveeno Colloidal Oatmeal in a lathering bar which is particularly well-suited to cleansing the sensitive skin of the atopic infant or child.

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References: 1. Sherman, W. B., and Kessler, W. R.: Allergy in Pediatric Practice. St. Louis, C. V. Mosby, 1957 (pp. 204-5). 2. Johnson, S. A. M.: J.A.M.A. *161*:1106, 1957. 3. Fisher, S.: J. Med. Soc. New Jersey *53*:592, 1956. 4. Ehrlich, R.: Am. J. Proct. *7*:497, 1956.

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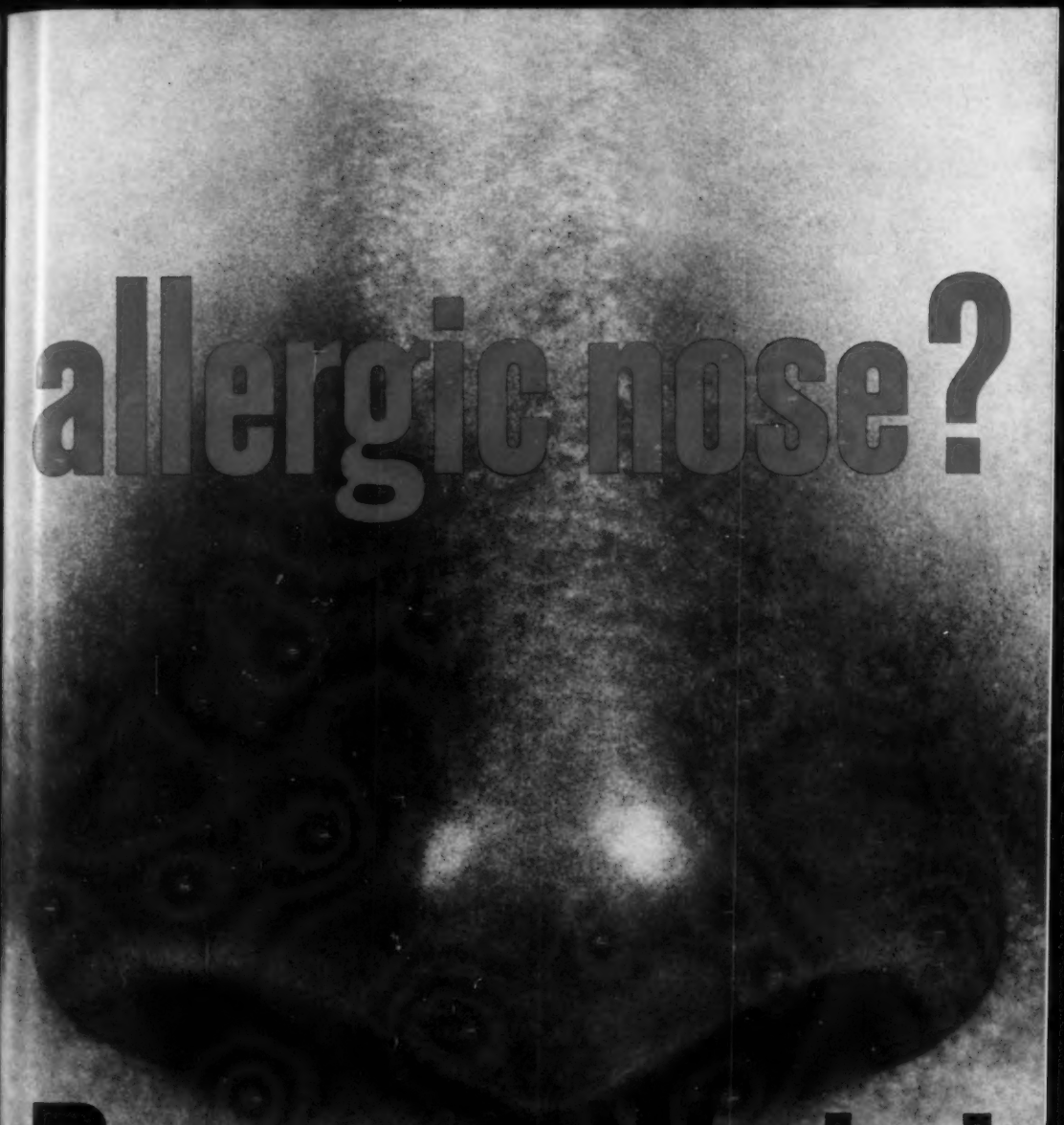

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with side effects as few as placebo

—New England J. Med. *261*:478, 1959 (Schiller, I. W. and Lowell, F. C.)

Dimetane works with an effectiveness of 91% in respiratory allergies —NEW YORK J. MED. *59*:3060, 1959 (Fuchs, A. M. and Maurer, M. L.).

In allergic and pruritic dermatoses the effectiveness rate of Dimetane is 94.6% —ANTIBIOTIC MED. & CLIN. THERAPY *6*:275, 1959 (Lubowe, I. I.).

The A. M. A. Council on Drugs characterizes Dimetane as demonstrating "...a high order of antihistaminic effectiveness and a low incidence of side effects." —J.A.M.A. *170*:194, 1959.

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...a highly potent, bactericidal antibiotic for combating staph and gram negative infections

...well tolerated when used on a properly individualized dosage schedule which does not induce excessive blood levels

"In many instances its effect has been dramatic and life saving . . ."[1]

"Six of the patients who survived were considered to be terminally ill at the time kanamycin was started but showed dramatic improvement and eventual complete recovery."[2]

"... indeed, the results [with kanamycin] are the most remarkable ever achieved with otherwise fatal staphylococcal infections that we have ever seen."[3]

"There appears to be no doubt that kanamycin has been lifesaving in those instances in which organismal resistance precludes the use of other antimicrobials."[4]

Information on dosage, administration and precautions contained in package insert or available on request.

SUPPLY: KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in vial containing 2 ml. volume. KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in vial containing 3 ml. volume.

REFERENCES: 1. Yow, E. M.: Practitioner 182:759, 1959. 2. Yow, M. D., and Womack, G. K.: Ann. N. Y. Acad. Sci. 76:363, 1958. 3. Bunn, P. A., Baltch, A., and Krajnyak, O.: Ibid. 76:109, 1958. 4. Council on Drugs, J.A.M.A. 172:699, 1960.

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For restoring and stabilizing the intestinal flora

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Mixed culture of Lactobacillus acidophilus and bulgaricus with metabolic enzymes naturally produced.

TABLETS & GRANULES

For gastrointestinal disturbances, diarrhea (antibiotic induced and others),[1,2,3] fever blisters and canker sores of herpetic origin.[4]

Usual dosage for adults and children: Four tablets or one packet of granules chewed and swallowed four times a day.

Supplied: Tablets in bottles of fifty—Granules in boxes of twelve one gram packets.

(1) Siver, Robert H.: Current Medical Digest, Vol. XXI, No. 9, September 1954. (2) McGivney, John: Texas State Journal of Medicine, Vol. 51, No. 1, January 1955. (3) Frykman, Howard M.: Minnesota Medicine, Vol. 38, No. 1, January 1955. (4) Weekes, D. J.: N. Y. State Journal of Medicine, Vol. 58, No. 16, August 1958.

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**Babcock, G., Jr., and Packard, L. A.: Clin. Med. 6:985 (June) 1959.*

CN-1401

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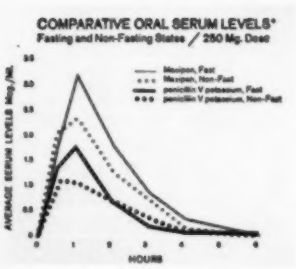
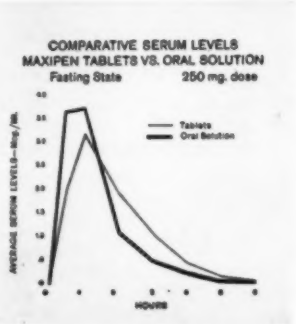


*Based on 3294 individual serum antibiotic determinations. Complete details on request.



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Focal Jacksonian	19	19 (100%)		

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1. Litchfield, H. R., et al.: New York J. Med. 50:2067, 1950.
2. Oberman, J. W., and Burke, F. G.: M. Ann. District of Columbia 23:483, 1954.

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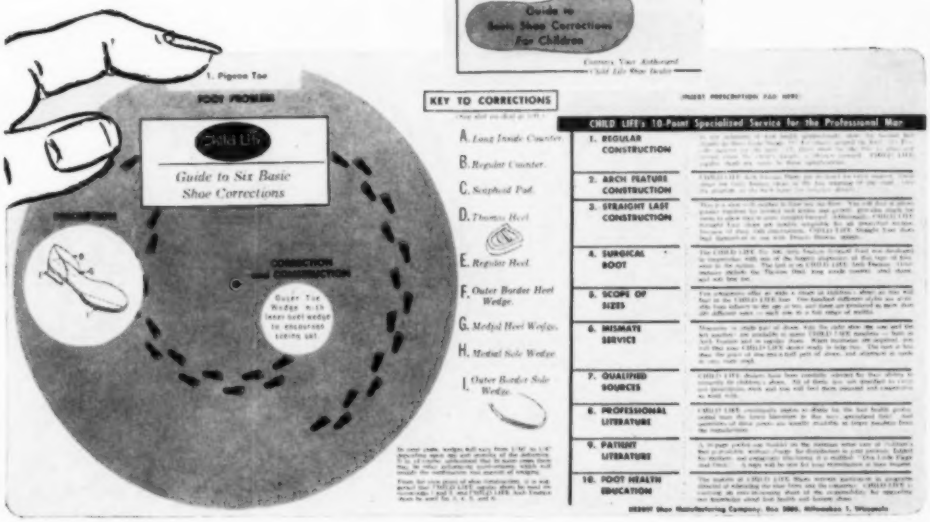

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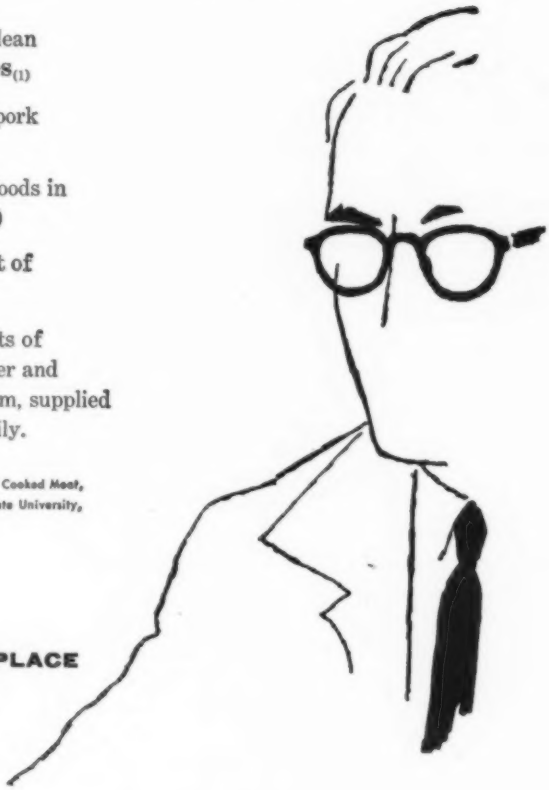

1. Leverton, R. M., and Odell, G. V.: The Nutritive Value of Cooked Meat, Oklahoma Agricultural Experiment Station, Oklahoma State University, Miscellaneous Publication MP-49, 1958.

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REFERENCES: 1. R. J. SCHNITZER, E. GRUNBERG, W. F. DeLORENZO AND R. E. BAGDON, ANTIBIOTICS & CHEMOTHER., 9:267, 1959. 2. R. C. V. ROBINSON, ANN. NEW YORK ACAD. SC., 82:(ART. 1), 144, 1959. 3. E. EDELSON, E. GRUNBERG, A. D. CALABRESE AND T. V. MORTON, IBID., P. 124. 4. P. L. WILLIAMS, IBID., P. 135. 5. F. T. BECKER AND J. L. TUURA, IBID., P. 131. 6. S. M. BLUEFARB, IBID., P. 119.

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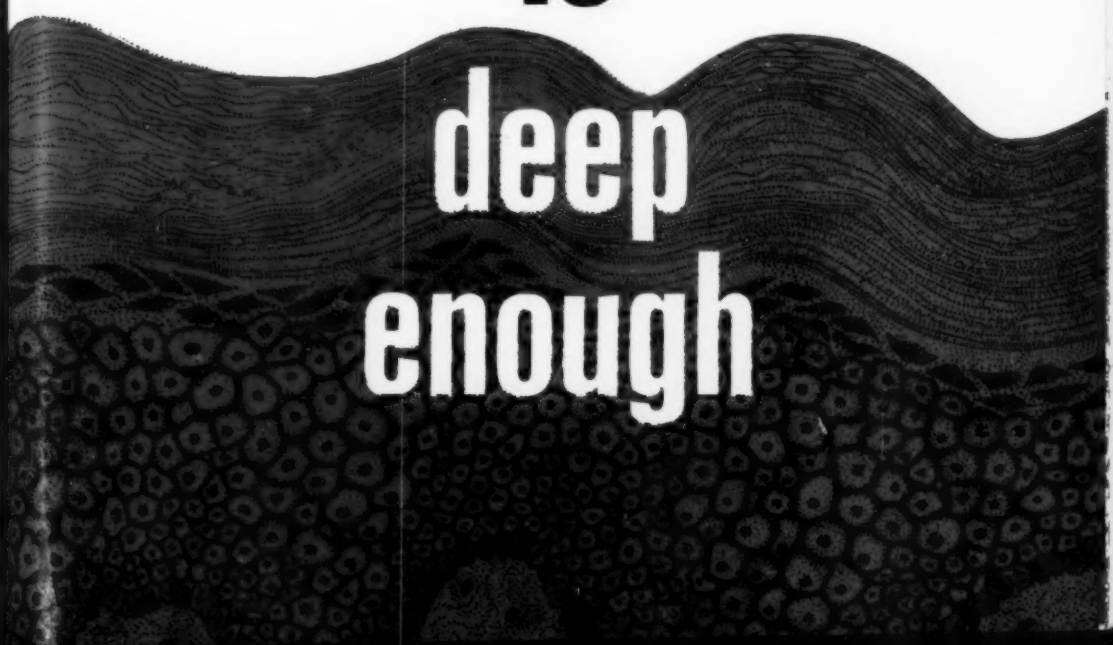

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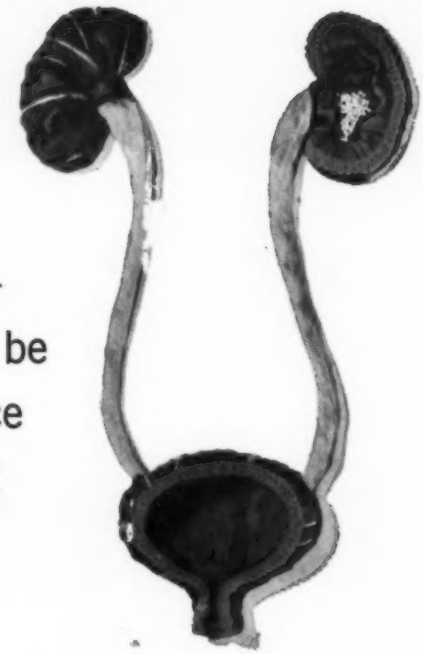

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REFERENCES: 1 Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

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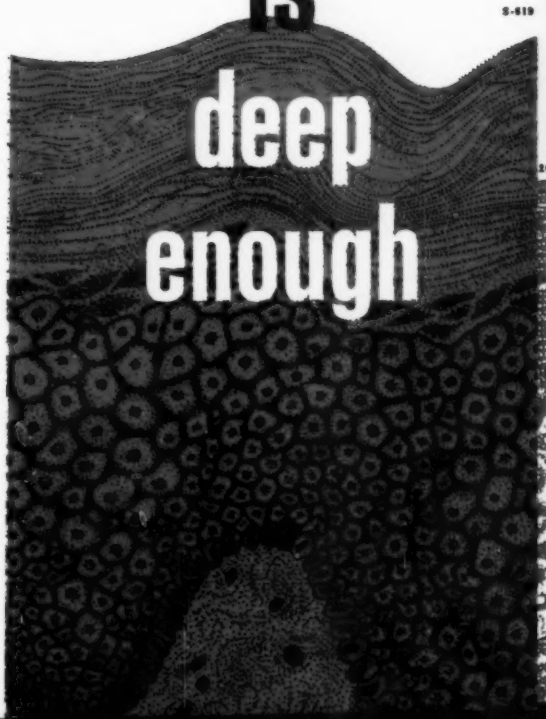

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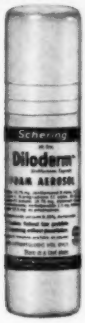

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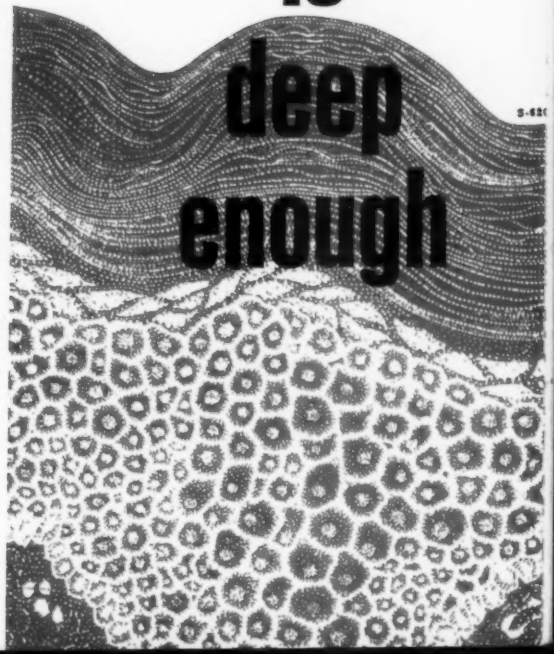

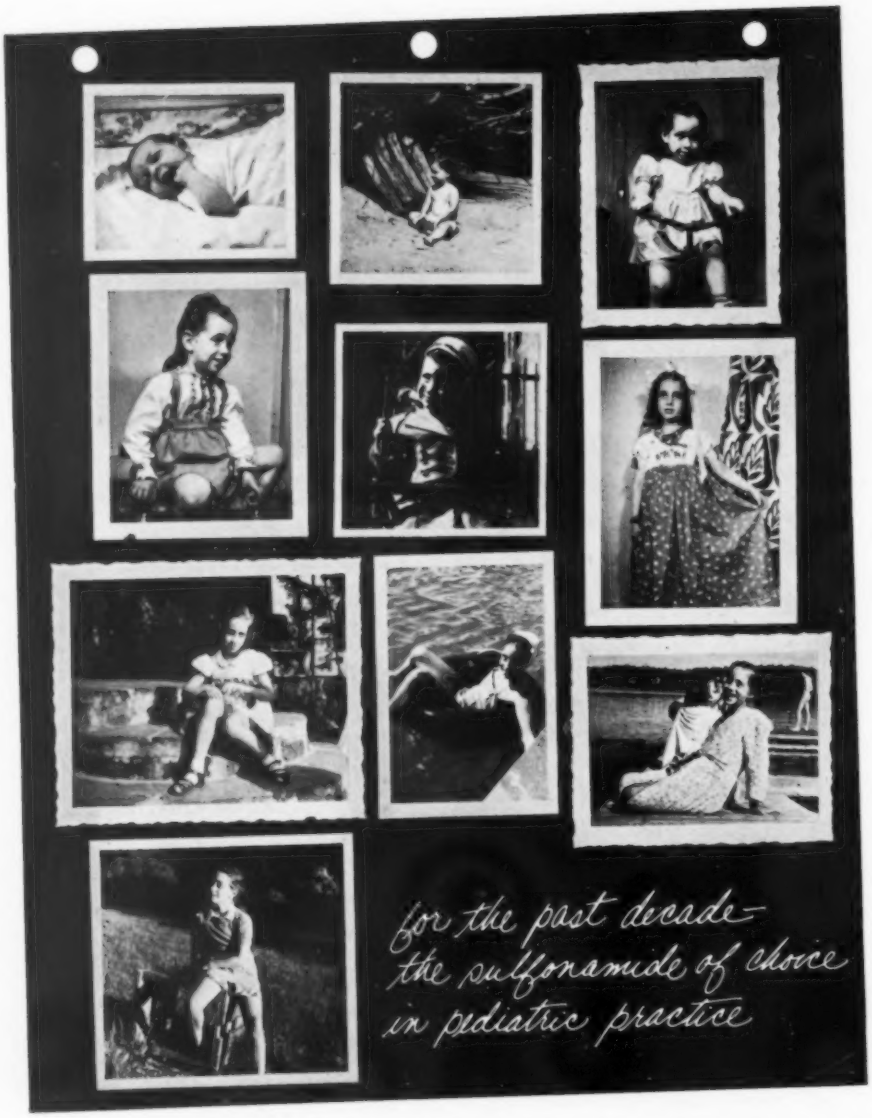

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Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

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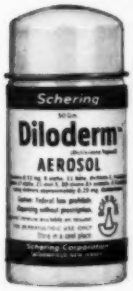

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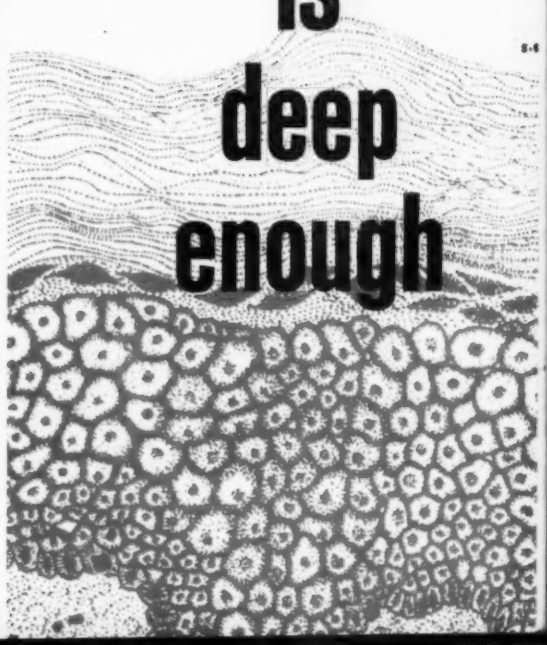

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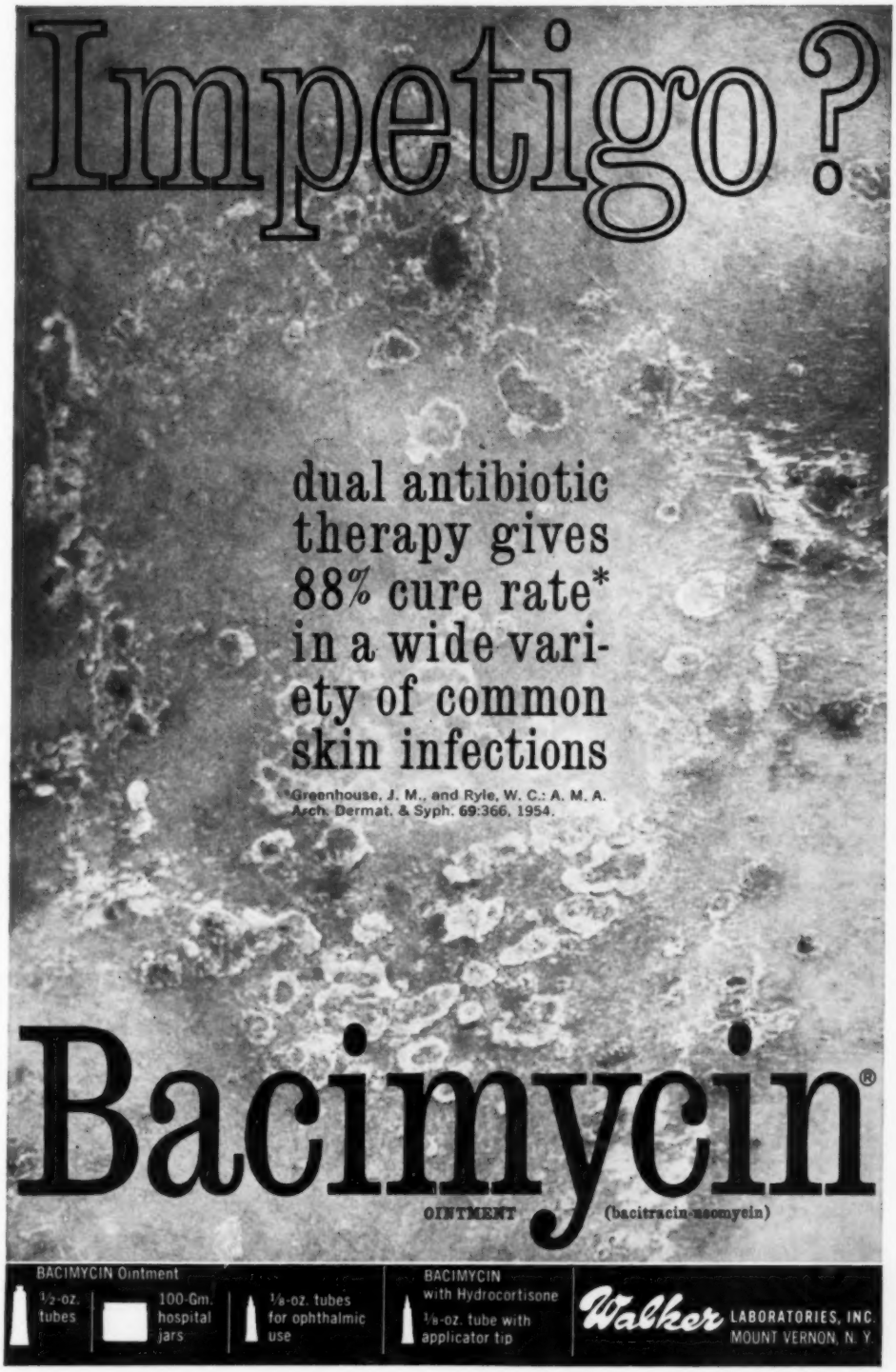
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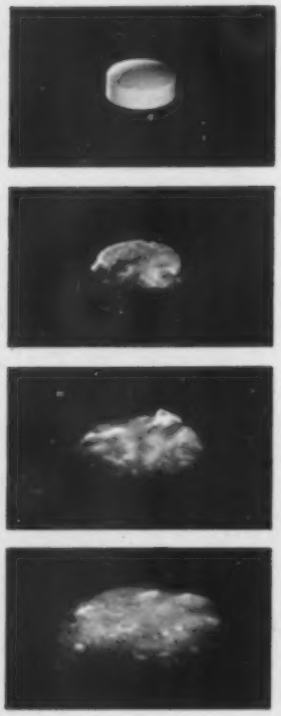

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1. Chow, B. F.: Gerontologia 2:213-221, 1958.
2. Committee on Nutrition: Pediat. 21:860 (May) 1958.
3. Chow, B. F., et al.: Am. J. Clin. Nutrition 6:386, 1958.

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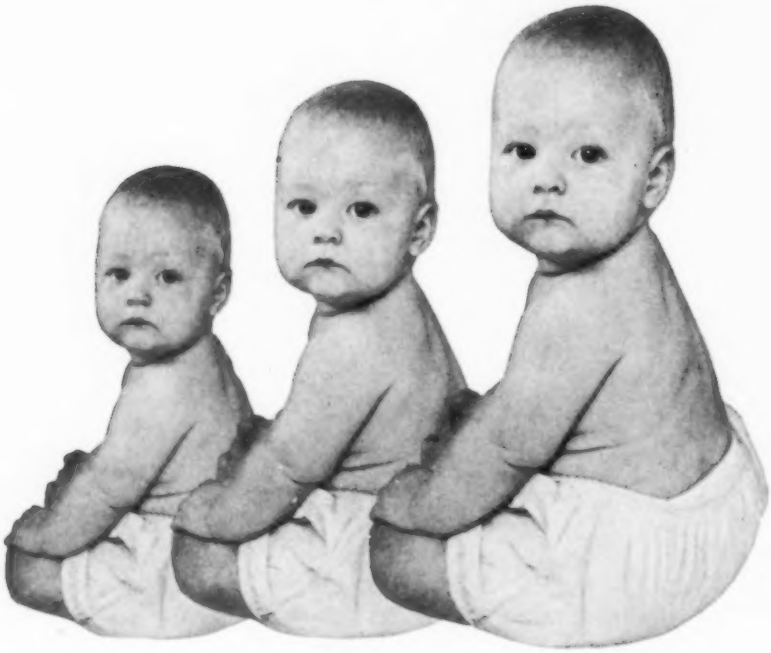

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ALTAFUR was found "highly satisfactory in most of the primary and secondary bacterial dermatoses treated to date," including "pyodermas . . . caused by antibiotic resistant strains of staphylococci."[1] In a nationwide survey[2] there were **94%** satisfactory results (cured or improved) among 159 patients treated with ALTAFUR for pyodermas.

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99.5% of isolates (214 of 215) from patients with staphylococcal infections—including many antibiotic-resistant strains—proved sensitive in vitro to ALTAFUR in tests conducted across the nation.[3] **99.7%** of staphylococcal isolates (334 of 335) at a large general hospital—including many antibiotic-resistant strains—proved sensitive in vitro to ALTAFUR.[4]

Wide, Stable Antimicrobial Spectrum

"Because of its relationship to previously developed nitrofurans, it is anticipated that [ALTAFUR] will retain its original spectrum after longstanding clinical usage."[5] Development of significant bacterial resistance to ALTAFUR has not been encountered to date.[6]

Minimal Side Effects

Side effects are easily avoided or minimized by these simple precautions: 1) *alcohol should not be ingested in any form, medicinal or beverage, during* ALTAFUR *therapy and for one week thereafter* 2) each dose should be taken with or just after meals, and with food or milk at bedtime (to reduce the likelihood of occasional nausea and emesis).

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1. Weiner, A. L.: Paper presented at the Conference on Recent Advances in the Treatment of Chronic Dermatoses, University of Cincinnati (Ohio), Nov. 5, 1959. 2. Compiled by the Medical Department, Eaton Laboratories, from case histories received. 3. Christenson, P. J., and Tracy, C. H.: Current Therapeutic Research 2:22, 1960. 4. Glas, W. W., and Britt, E. M.: Proceedings of the Detroit Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959, p. 14. 5. Leming, B. H., Jr.: Ibid., p. 22. 6. Investigators' reports to the Medical Department, Eaton Laboratories.

Tablets of 250 mg. (adult)

and 50 mg. (pediatric)

bottles of 20 and 100

Altafur®

NITROFURANS . . . a unique class of antimicrobials

EATON LABORATORIES, NORWICH, NEW YORK

Vesprin

Squibb Trifluprомazine Hydrochloride

controls anxiety and tension in everyday practice

Doctor...
I can reason
with him on
other problems...
but not when
it comes to
eating

In pediatric practice, as well as in general medical practice, many children with behavior problems can benefit from the administration of VESPRIN, a full range tranquilizer with minimal toxicity and side effects. Equally important to the physician is the fact that VESPRIN does not produce somnolence while retaining high potency as a tranquilizer – even in low dosage.

Consult Vesprin package insert or PDR for indications, dosage and directions for use. Supply: for oral use—tablets containing 10, 25 and 50 mg. SQUIBB *Squibb Quality – the Priceless Ingredient*

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From Procter & Gamble:

Protection against Diaper Rash*

with new

Germaseptic dreft

* externally caused

1. ***New:*** Procter & Gamble has developed a new detergent, Germaseptic Dreft, containing TCC—3,4,4′ Trichlorocarbanilide, an effective bacteriostatic ingredient. This special ingredient helps prevent the growth of germs on diapers and baby clothes.

2. ***Effective:*** Radioactive tracer studies show that TCC adheres to fabrics during washing, and bacteriological tests prove that TCC *stays* active in preventing germ growth even through normal rinsing, drying, storage and wear.

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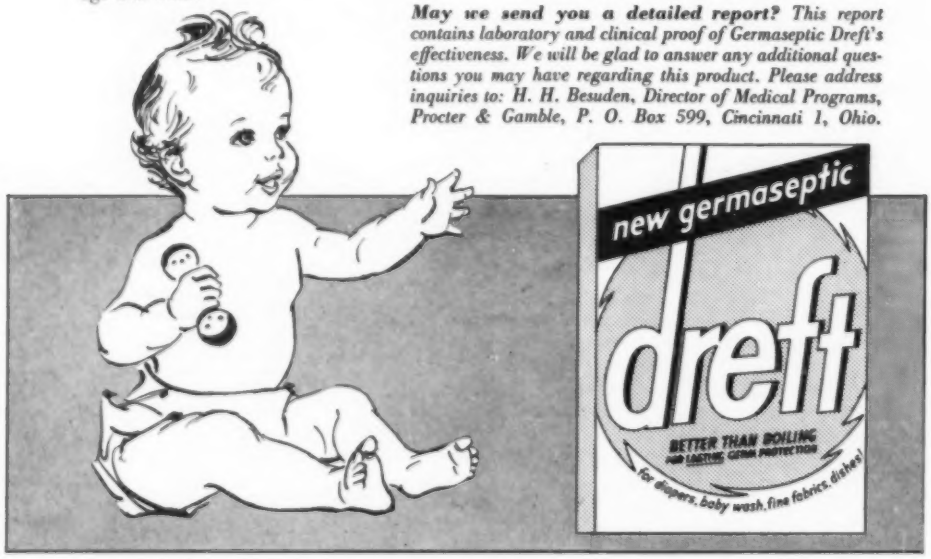

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vomiting quickly controlled rectally

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Supplied in jars of 12.
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The "Neocera" Base Makes the Difference

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for individualized management
of cow's milk sensitivity

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LIQUID / POWDERED

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Liquid — 15½-fl.oz. tins; **Powdered** — 1-lb. tins.

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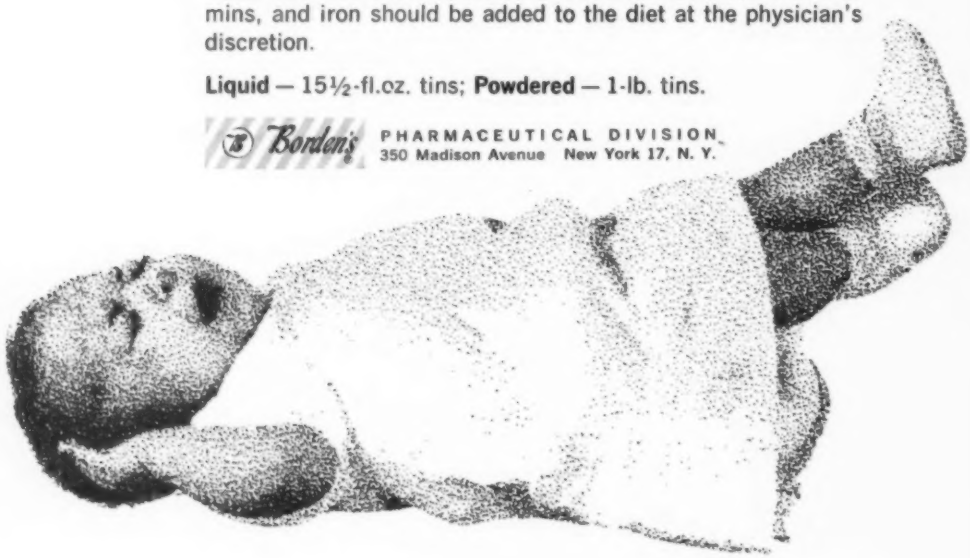

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